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AN APPRECIATION OF FRANK N. WILSON, M.D.

FRANK N. WILSON, M.D., Professor of Medicine, University of Michigan, on Nov. 19, 1950, has completed 60 years of a most fruitful scientific life. On this day, birthday greetings and best wishes from a host of appreciative and admiring friends, respectful colleagues, and devoted pupils will travel from around the face of the globe to Ann Arbor. Many of his students will think reverently of the great inspiration and again be in Ann Arbor in spirit. Dr. Wilson has been the inaugurator of the modern era of electrocardiography and exponent of the present concepts of the significance of changes in the ventricular complex. As the Wilson era dawned, the Sir Thomas Lewis era of electrocardiographic study of the mechanism of cardiac disorders closed. The Willem Einthoven era began when that ingenious Dutch physiologist built and applied the delicate string galvanometer to the studies of the electrical phenomena of the heart. The Viennese school under Rothberger and the London school under Lewis had made extensive clinical and experimental studies with the instrument.

Dr. Wilson was graduated from the University of Michigan Medical School in 1913. He served an internship at the University Hospital, took an assistantship under Dr. A. W. Hewlett, and began his work in clinical cardiac physiology which he has pursued unwaveringly all of his life. He was the youngest of a group of American cardiologists chosen to work with Sir Thomas Lewis at the British Heart Hospital in Colchester during World War I. These were most inspiring years for Dr. Wilson. After World War I, he joined the staff of Professor George Dock at Washington University as instructor in Medicine and director of the Heart Station. I had the good fortune to be accepted as his assistant in this station. This was an unparalleled experience. One morning, after a long night vigil, we excitedly announced to Dr. Dock that we had made an ante-mortem diagnosis of coronary thrombosis and cardiac infarction with the help of the electrogram. Dr. Dock exclaimed: "Great scott, I did that before you boys were born." He brought out a reprint from Ann Arbor to prove it and characteristically deflated our ego. Two years of intense experimental and clinical work in the Washington University Heart Station were interrupted when Dr. Wilson was invited to return to Ann Arbor as Associate Professor of Medicine. In Ann Arbor he worked over the material gathered in St. Louis for two years before he was able to get a string galvanometer with which to continue his studies.

He also buried himself in the studies of electrophysics and mathematics which he felt he needed in the prosecution of his work.

The first string electrocardiograph arrived in Ann Arbor in 1922, and no room could be found for it in the old hospital. The only space available was under the wooden stairway which led to the main medical amphitheater where George Dock and A. W. Hewlett had held forth. This was the Heart Station for the several years until the new hospital was built. There were no windows, and in this cranny a dark room was built between the old walls, but Dr. Wilson, immune to disappointments, was high in spirits. The noise and dust raised by the trampling feet of medical students on the stairway, which served as a roof and back wall of the Heart Station, never disturbed Dr. Wilson. He was oblivious to the bedlam when he was in thought, and he was wrapped deep in thought most of the time. The shell of the great new hospital for which he worked out plans for a modern Heart Station was boarded up for four long years.

He put to objective experimental test the ideas that he had worked out in his mind. He was not content with some of the preliminary data that he had obtained in St. Louis several years previously. Again obstacles arose. Ill health forced him to take a year's leave of absence, but he made the most of this time and gained the mastery of higher mathematics which he needed for his meticulously planned experiments. He became so proficient that he could predict mathematically the outcome of many experiments. Yet so thorough was he that many experiments had to be done and redone and rechecked so that there could be no possibility of error.

He presented his work before the American Society of Clinical Investigation and the Association of American Physicians, but he always had so much new data that he could barely get the background for his presentation under way in the ten or fifteen minutes allowed. He was usually thinking so far in advance of the general internists and cardiologists that for years only a few could comprehend and realize the fundamental value and significance of his work.

Sir Thomas and Lady Lewis traveled to Ann Arbor obstensibly to photograph Michigan water fowl and incidentally to discuss electrocardiography. Professor Willem Einthoven was also in Ann Arbor to discuss "Fine Fibers in Physiology" and planning to build a rugged pair of galvanometers in tandem for Dr. Wilson, when he was notified of his election as Nobel prize winner in Medicine and Physiology. Professor Einthoven's modest acceptance of the honor was most impressive.

In spite of the many obstacles and years of waiting, little support with few plaudits from the masses, and the faith of only a few, Dr. Wilson persisted in his studies of the ventricular complex, certain in his own mind of the significance of his work. Gradually he solved the fundamentals of the problem of bundle branch block on which he had started to work ten years previously in St. Louis. The subject of interventricular conduction disturbance became clear even to the general internist as Dr. Wilson demonstrated his theory of the negativity of the ventricular cavity, activated at the endocardial, progressing to the epicardial surface with the inscription of the intrinsic deflection as the impulse arrived at

the epicardial surface of the heart. He proved in various animal studies and in observation on many patients the value of the unipolar exploring electrode with the whole body connected to a central terminal as the indifferent electrode. This created the new era in experimental and clinical electrocardiography. It finally became evident to cardiologists and internists that Dr. Wilson's experimental and clinical studies had broadened the scope of electrocardiography and had made it possible to determine the exact location, extent, age, and progression of practically all types of myocardial infarction.

Internists as well as cardiologists learned and realized that they had to master the new concepts in order to practice medicine scientifically. Students from the Old World as well as from the Americas and Canada came to his laboratory to learn the fundamental science and return to their own states and countries with the new knowledge. These inspired and enlightened students were trained in the clear concepts of basic physics and mathematics on which Dr. Wilson had so firmly established his work. The laurel wreaths and accolades from Central and South American Republics came to him during the last decade.

Dr. Wilson has been the typical absent-minded professor, totally absorbed in his thoughts and often losing his way in walking or driving to his home in Ann Arbor. He usually seems to pay little attention to what is going on about him, but, nevertheless, he is a kindly human being and a most congenial friend with a ready smile and word of encouragement. The personal *esprit de corps* in his laboratory among his fellow workers and students is always high. His friendship is enduring. He has held the absolute respect of his associates and is always conceded to be thinking several steps ahead of his staff. He never practices showmanship or bluff and has no interest in publicity, medical politics, wide acclaim, or personal aggrandizement. He is a quiet, modest worker, at ease anywhere.

Most of his important contributions have appeared in this JOURNAL. The Editor, who suggested this tribute and assigned the pleasant duty, and the Editorial Board hope to be included among his intimate friends in the Americas and in the world at large and join in sending warm greetings and sincere good wishes to him on this, his sixtieth birthday. The C. V. Mosby Company joins in respectfully dedicating this November, 1950 number as a *Festschrift*, a small token of appreciation of the permanent eminence of Frank N. Wilson, M.D., in the field of cardiovascular investigation and practice.

GEORGE R. HERRMANN, M.D.

Original Communications

THE LEFT INTRAVENTRICULAR POTENTIAL OF THE HUMAN HEART

I. Method

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THE first paper on catheterization of the left ventricle of the human heart was published by Zimmerman and co-workers.[1] They were able to catheterize the left ventricle only in patients with aortic insufficiency of syphilitic origin, but they failed to do it in five normal subjects. These authors thought that during systole the normal aortic orifice is not sufficiently opened to allow the passage of the catheter. They recorded a case of death by ventricular fibrillation probably due to the catheter entering a coronary vessel.

Studies on catheterization of the left human ventricle were started by Limón and collaborators in 1947[2] at the National Institute of Cardiology. By the end of 1949, Limón had reached the left ventricular cavity in twenty-eight subjects, and in a recent publication[3] he reported seventeen patients who were catheterized via the radial artery with no accidents. The studies of Limón in human beings were preceded by experiments in dogs in order to know, first, whether the arterial catheterization caused any arterial or valvular lesions, and, second, whether the passage of the catheter would provoke arterial spasms which would prevent the experiment. No lesions were found in the arteries or aortic valves of the animals. Moreover, the Mexican authors were able to catheterize the left ventricle in several subjects with no cardiac disease.

In view of the above results, it was decided to study the left intraventricular potential in the human heart. The present paper deals with the method used in the first twenty-five patients including normals, hypertensive subjects, and those with aortic insufficiency of syphilitic or rheumatic origin.

In the subjects chosen for catheterization we excluded all those who showed any one of the following: signs of cardiac insufficiency, gallop rhythm, clinical or electrocardiographic signs of coronary insufficiency (one had possible anterolateral ischemia), active rheumatic carditis, subacute bacterial endocarditis, signs of recent embolus, auricular fibrillation, or other rhythmic disturbances, such as repeated extrasystoles.

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In previous publications[4] the technique for intravenous cardiac catheterizations was described. For electrocardiographic explorations of the left ventricle, ureteral catheters (Cournand) numbers 6 and 9 were used. In the lumen they have a fine silver wire whose contact surface is situated 1 or 2 mm. above the distal end. The site of preference for entering the arterial tree is the radial artery in the region of the cubital fossa, immediately after its origin, below the aponeurosis of insertion of the round pronator muscle. The right radial artery should be used if possible. The reasons for this will be discussed later. At times, the course of the artery is difficult to see, and usually its pulsation is visible only in certain types of cases, such as aortic insufficiency and hypertension; therefore its location usually has to be determined by palpation. Once localized, the course of the artery for 2 or 3 cm. should be marked by the scalpel before infiltrating the tissues with local anesthetic. We use 2 per cent Novocain, making sure that the anesthetic reaches the deep planes on which the artery lies. This is done under strict asepsis. The dissection of the artery is a bit more difficult than that of the vein, since for most of the dissection, the only guide is palpation. It must be remembered that the artery is located below the aponeurosis of insertion of the round pronator muscle, surrounded by adipose tissue, accompanied by two veins, and located at one side of the median nerve. This relation to the nerve is very important, since the careless handling of the nerve can cause the patient severe pain. When the artery is dissected free, it is isolated between two strands of catgut in order to facilitate its manipulation.

In practically all cases, the lumen of the artery can be reconstructed at the end of exploration. In order to facilitate this, the incision made in the wall of the artery should be just large enough to permit the passage of the catheter. The artery is punctured initially using a transfusion trocar. The opening is then enlarged slightly with the scalpel. The catheter, previously lubricated with petroleum jelly, is then passed without difficulty. At times marked muscular spasm in the region of the surgical opening is such as to prevent the passage of the catheter. If the procedure is suspended for several minutes or if 0.03 or 0.05 Gm. of papaverine is given intravenously, this difficulty can be overcome. (Dr. Limón thinks that the papaverine is not useful for release of the spasm.) Somestimes it is necessary to apply hot packs over the artery.

Normally, there are three anatomical obstacles that obstruct the passage of the electrode. The first is encountered at the level of the clavicle and is overcome by abducting the arm to 90 degrees, or with the arm in this position, by moving it up and down. The second obstacle is met at the beginning of the brachiocephalic trunk, where the catheter frequently curves upward and passes into the internal carotid artery. To avoid this, the catheter should be rotated and pushed while the patient is taking deep breaths. The deep inspirations and expirations elevate and lower the vascular pedicle, thereby aiding the passage of the catheter to the ascending aorta. Not infrequently during these maneuvers, the catheter will pass to the descending aorta, an occurrence that is observed most frequently when the catheterization is initiated in the left radial artery. For this reason the right radial artery is the site of election.

The passage of the catheter through the aortic valves to the ventricular cavity is more difficult. It has a tendency to stop and curve, and one has to be extremely careful not to force it into one of the coronary arteries. At this point, the catheter is kept straight and free of slack, and when the tip touches the valves, it is drawn back very slightly, and gentle push and pull movements are exercised until it passes into the cavity.

After the electrode is withdrawn, the opening in the artery is closed with two or three sutures of silk. It is not always possible to make a complete restoration of the wall of the artery, and in case of doubt, we prefer to ligate on both sides of the opening, because of the possibility of hemorrhage. This procedure, which apparently could cause serious disturbances in the circulation of the part, actually carries little risk. The significant anastomoses of the radial and cubital arteries in the palmar arch assure an efficient circulation. At times, before closing the vessel it is possible to observe that the distal portion bleeds quite as freely as the proximal. When it is practicable to do a good arteriorrhaphy, the arterial pulse can be perceived after the closure.

All of our patients were hospitalized, and for the three days following the procedure were given 50,000 units of penicillin every three hours, and 100 mg. of heparin intramuscularly every twenty-four hours. This treatment is clearly indicated because of the recent findings[5] of arterial thrombosis in normal dogs following arterial cardiac catheterization. On the fifth day the clips are removed from the wound, and the patient is discharged if there are no complications.

In our series, the catheter followed an apparently paradoxical course in two patients, in that it described a convex line to the right, approaching the right border of the heart. In the first patient, we thought that the catheter had entered the right internal mammary artery, a possibility that was discarded after viewing the patient in various positions and observing that the catheter remained within the cardiac shadow. In the second patient, when the catheter took this anomalous course, the patient complained of intense anginal pain which disappeared when the catheter was withdrawn to a position above the aortic valves. We believe that in both patients the catheter entered the right coronary artery, and that the abrupt diminution in the amount of blood going into the artery occasioned the anginal crisis that the second patient suffered. Fortunately, the catheter was withdrawn in both cases before the patient suffered irreversible consequences. In the days following catheterization, both patients were followed with numerous electrocardiographic studies.

After the above two incidents occurred, we were particularly careful to withdraw the catheter immediately whenever it appeared to be taking such a course. It is possible that the sudden death which some investigators have recorded during this procedure can be attributed to catheterization of a coronary artery.

Aside from the occurrence already related, there is always the possibility of paroxysmal tachycardia or bursts of extrasystoles, just as are met with in intravenous cardiac catheterizations, and which can be overcome by withdrawing the electrode from its contact with the wall. It is worth mentioning that the ectopic beats are encountered particularly when the electrode is in contact with

the higher portions of the interventricular septum, as is equally true in the right ventricle. We should point out another condition that occurred in two of our patients in whom the catheterization had been unduly prolonged. This consisted of an acute pain in the cubital fossa, apparently inexplicable in that it did not respond to additional and careful infiltrations of Novocain. On the other hand, it disappeared readily when the forearm was flexed on the arm. In all our cases, we place a pillow under the elbow of the patient, which puts the arm in a position of hyperextension, and which undoubtedly causes a certain degree of stretching of the nerve trunks. If this is prolonged sufficiently, it is possible that it produces the disturbance, noted in these two patients, which disappeared with the simple correction of the position.

In our department we have done twenty-five arterial cardiac catheterizations and with the exception of one patient, there were no important complications which could be attributed to the procedure. There were certain local sequelae inherent in the local surgical procedure, such as induration in the area of the wound and pain because of the unanatomical position of the arm during the procedure.

The one fatality in this series was a patient with syphilitic aortitis and aortic insufficiency. There was no evidence of cardiac insufficiency. The procedure was performed without incident, and in the subsequent days there was nothing to suggest anything untoward in the patient's condition. On the third day, without any premonitory signs, he suddenly died. The family refused to give permission for necropsy, and we were unable to determine the precise cause of the patient's death.

In several subjects we were able to catheterize both ventricular cavities. The tip of both catheters was placed at the same level of the interventricular septum. In this manner we could obtain transeptal bipolar leads. This procedure was found very helpful to discover minimal grades of incomplete left bundle branch block.

The main difference between our technique and that proposed by Limón and associates concerns the manner in which the catheter is introduced through the aortic cusps. In order to avoid the obstruction of a coronary vessel with the catheter, they have devised the following maneuvers: Before the catheter is introduced, it is kept wrapped around a ball of gauze in order to form a small loop at the tip. This loop is straightened out as the catheter passes through the small arteries, but as soon as it enters larger vessels the loop forms again. If the catheter tip arrives at the site of the aortic cusps with a loop of small diameter, the catheter is introduced directly, in such a way that the elbow of the loop is the first to enter the ventricle, just as if a hairpin were to be introduced into a bottle. In this way it is practically impossible to catheterize a coronary artery. If the catheter arrives at the site of the aortic cusps with a loop of a wider radius, i.e., if the tip forms an "L" instead of a "J," then the short end of the loop is placed on the tip of the cusps, and the catheter is maneuvered in such a way that the tip enters the ventricle more of its own accord than by one's efforts.

Since they catheterize the left ventricle in order to register pressure tracings as well as the electrocardiogram, they add the following precaution: When the

catheter is about to enter the left ventricle, they connect it to the manometer. In this way they are able to detect if the catheter tip is entering the ventricle or a coronary vessel. In the first instance, the diastolic pressure drops to zero, whereas in the second, it remains high.

SUMMARY

A method for the catheterization of the left ventricle is described. This method has been applied to the study of the left intracavitary potential. Twenty-five subjects were studied. These included normal subjects, hypertensives, and patients with syphilitic aortic insufficiency and rheumatic mitral lesions. One patient died three days after the study. The cause of death could not be determined, since no post-mortem examination could be done.

By catheterization of both ventricular cavities and the use of bipolar transeptal leads, it is possible to study the action current of the interventricular septum.

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THE LEFT INTRAVENTRICULAR POTENTIAL OF THE HUMAN HEART

II. Criteria for Diagnosis of Incomplete Bundle Branch Block

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UP TO the present, a QRS duration of 0.12 second or more has been a requisite for the diagnosis of complete bundle branch block. Incomplete BBB must be considered when the duration of the QRS complex is between 0.10 and 0.12 second, and the morphology of the tracing is suggestive of BBB. This concept, which can be considered the classical one, has many limitations, and we believe it should be abandoned. Actually, the value of 0.12 second, which distinguishes complete from incomplete BBB, depends, in addition to the degree of block, on the size of the heart and the age of the subject, as well as other factors. In many patients in whom the diagnosis of complete BBB has been made, it has been observed that over a period of years the duration of the QRS complex continues to increase, at times to 0.15 or 0.16 second or even more. Are we to assume that these new figures indicate a greater degree of bundle branch block? If so, we should change our definition of complete BBB. On the other hand, there are many published cases which show only changes characteristic of left ventricular hypertrophy with the duration of the QRS complex greater than 0.12 second.[1]

With regard to incomplete BBB, we can affirm that it is recognizable even though the duration of the QRS complex is less than 0.10 second, that is, 0.08 or 0.09 second. In the dog it is relatively easy to produce incomplete BBB.[2] To do so, a slender round-pointed probe is passed through the free wall, right or left, according to which block is wanted, until it reaches a point high in the interventricular septum where the bundle branch begins its descent. This point is tapped repeatedly with the probe until BBB is produced. In the majority of cases such a block is transitory, lasting from a minute to several hours, and after its disappearance, the tracing does not immediately assume the morphology of the control tracing, but rather, a number of transitional complexes are registered—ten to twenty or more—with the QRS complex duration becoming progressively less, e.g., 0.11 second, 0.10 second, 0.09 second, 0.08 second, 0.07 second, etc., which correspond to incomplete BBB.

In human beings also, incomplete BBB has been described,[3,4,5] and even recently, incomplete right BBB with a QRS complex duration of less than 0.10

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second is mentioned.[4] The diagnosis of this type of block is made, not by the duration of the ventricular complex, but by the appearance of two positive deflections, R and R′, in the right precordial leads.[2] We agree with this concept, and in the interpretation of our tracings we consider the morphology to be much more important than the duration of the complexes. For the diagnosis of incomplete right BBB, we pay particular attention to the registration, or the tendency toward registration, of two positive deflections, R and R′, in right precordial leads V_1 and V_2, or at points even more to the right.

Basing our opinion on the studies of right intraventricular potential with simultaneous registration of right precordial leads, we believe that those complexes transitional between those of normal subjects and patients with complete right BBB have the morphology represented in Fig. 1. This is for right precordial leads registered with the central terminal (V_1 and V_2).

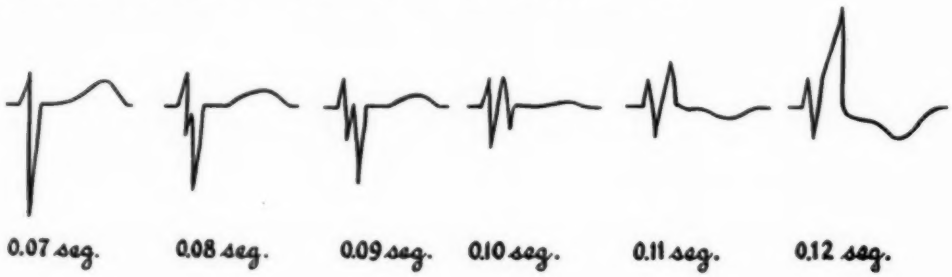

Fig. 1.—Complexes in V_1, transitional from normal tracing to complete right BBB. The intermediate tracings correspond to incomplete right BBB.

It must be admitted that two positive deflections in V_1 and V_2 do not necessarily represent right BBB, because there is the possibility that complexes with two positive deflections occur on the epicardial surface of the free wall of the right ventricle in the normal human heart. However, up to the present, the epicardial surface of the normal human heart has not been explored with adequate techniques. Those studies carried out on patients undergoing pneumonolysis[6] were done at a distance from the heart and on hearts which possibly were abnormal, in which case a certain degree of right BBB would not be unusual. Direct explorations in patients with constrictive pericarditis or traumatic wounds of the heart cannot be considered as being normal. For the foregoing reasons, we always consider a double positivity in V_1 and V_2 as due to right BBB.

There are patients with right BBB in whom the two positive deflections are not seen. This is because the corresponding precordial points are not facing toward the right ventricle, but rather toward the interventricular septum, or to the left ventricle, or to the right auricle. We published[7] a case report of right BBB in which all six precordial leads showed complexes of the left ventricular type. The diagnosis was made by the standard and unipolar limb leads. If the electrodes of V_1 and V_2 register the right auricular potential, the initial positive deflection is lacking, and the complexes are of the qR type with the positive deflection wide and slurred by the block. One has to be able to recognize

this type of tracing in order to avoid making the diagnosis of anteroseptal infarct with right BBB. We also published a case[7] of incomplete right BBB with two positive deflections in V_5 and V_6 and with complexes of the qR type from V_1 to V_4. By cardiac catheterization and angiocardiographic studies, it was possible to demonstrate that the first four precordial leads were oriented toward the right auricle and that V_5 and V_6 were oriented toward the right ventricle. Moreover, the form of the ventricular complex in right or left BBB in each of the ventricles is not the same for different points on the epicardial surface of the heart. In dogs, the form of the ventricular complex is not the same in the trabecular zone and in the pulmonary conus of the right ventricle, nor is it the same in the apex and in the thick portion of the lateral wall of the left ventricle. Many other points may be taken into consideration, but the aforementioned suffice to emphasize the necessity for a complete study of all leads and a careful consideration of the position of the heart and of the orientation of the electrodes.

Recently, Wilson[3] expressed the opinion that a slight degree of right BBB is a normal finding in the human heart. This assertion is based on the fact that, generally speaking, the total normal septal activation in the human heart proceeds from left to right, and the vectors that represent this activation cause an initial positivity in the cavity of the right ventricle and an initial negativity in the cavity of the left ventricle. In the dog's heart, septal activation proceeds similarly. We will not discuss the causes that have been invoked to explain the predominance of left-to-right septal activation. However, we do not believe that this should be considered a slight degree of right BBB, and we reserve the term to use when a second positive deflection is inscribed in the right precordial leads and in tracings from some place in the cavity of the right ventricle.[8] Moreover, if there is not predominance of left to right in septal activation and the activation proceeds equally in both directions, a condition recognized by the presence of wholly negative complexes in both right and left ventricular cavities, to us it seems correct to speak of a slight degree of *left* BBB. Later on, we will see that this concept is strengthened by the study of the intracavitary potential in the human heart.

Taking into account the better understanding of right BBB that resulted from the study of right intraventricular potential,[8] we undertook in the present study to investigate the form of the tracing in the cavity of the left ventricle, hoping that the results would help to clarify the problem of incomplete left BBB.

It is well known that the normal left intraventricular tracing in the dog's heart is entirely negative and of the QS type. After the left branch has been cut, the complex shows an initial positivity and is of the RS type. In incomplete left BBB of the same animal, the transitional complexes show a progressive diminution of the initial positivity (R wave) until the tracing reverts to normal, or QS. Theoretically then, one should except tracings taken from the left ventricular cavity of man in incomplete left BBB to show changes similar to those found in the dog in the same anomaly of conduction.

The study of septal activation and the recognition of the degree of block can also be done by placing an electrode in each ventricle, adjacent to the interventricular septum. By means of a bipolar lead, the direction, in general terms,

of septal activation at the level where the electrodes are placed can be determined. In order to be sure that this procedure was correct, two electrodes were placed in the heart of the dog, one in each ventricle, near the septum. Their position was controlled by fluoroscopy. Lead II of one of the channels of a Sanborn Poly-Viso was used; the left leg electrode was placed in the right ventricle and the right arm electrode in the left ventricle. In this way, if the direction of the vectors across the septum is from left to right, the tracing registers positivity.

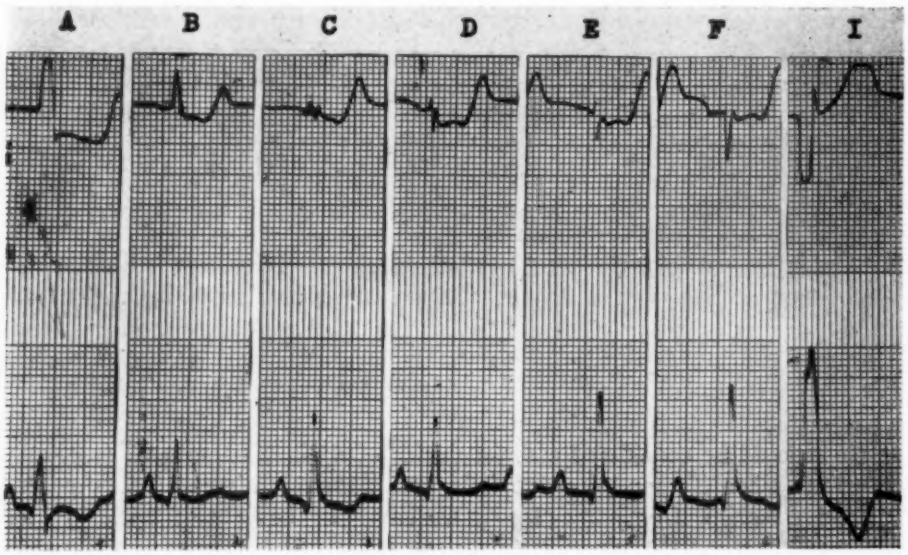

Fig. 2.—Complexes taken by a bipolar lead across the interventricular septum (upper tracings). The positive electrode was placed in the right ventricle and the negative one in the left ventricle. An ordinary Lead II tracing was taken simultaneously (lower tracings). In the control tracing (*B*) the QRS complex of the bipolar lead is wholly positive and has a duration of 0.03 second. After the right branch was tapped (*A*), the complex widened to 0.05 second, and the voltage increased slightly. After the right block disappeared, the left branch was tapped until left BBB appeared. In left BBB of slight degree (*C*) the complex of the bipolar lead is polyphasic and of a very low voltage. The degree of block increased in tracings *D*, *E*, and *F*, and there was recorded progessively greater negativity. In the last tracing (*I*) Lead II is very characteristic of left BBB, and the bipolar complex is very wide with a total duration of 0.07 second and with marked negativity.

At the same time that this bipolar lead was registered, an ordinary Lead II tracing was taken in another of the channels of the apparatus (Fig. 2). In the control tracing (Fig. 2, *B*) the QRS complex of the bipolar lead is wholly positive and has a duration of 0.03 second. The T wave is diphasic. After the right branch of the bundle of His was tapped (Fig. 2, *A*), the complex widened to 0.05 second and the voltage increased slightly. The negative areas of RS-T and T increased. Lead II, taken simultaneously, is very characteristic of right BBB. After the right block disappeared, the left branch was tapped until left BBB appeared and various transitional forms were registered. In left BBB of slight degree (Fig. 2, *C*) the complex of the bipolar lead was polyphasic and of a very low voltage, which suggests that septal forces were practically neutralized at the level of the exploring electrodes. The positivity of T had increased slightly.

In Lead II taken simultaneously, the voltage of R had increased, and the negative area of T was greater. The Q wave persisted, but this is a common finding in left BBB in the dog. The degree of block increased in tracings *D*, *E*, and *F* of Fig. 2; because of this, there was recorded progressively greater negativity in the bipolar lead, and the T wave showed greater areas of positivity. In Lead II taken simultaneously, the voltage of R increased, and there was also an increase in the negativity of T. In the last tracing (Fig. 2, *I*) Lead II is very characteristic of left BBB, and the bipolar complex is very wide, with a total duration of 0.07 second and with marked negativity. The area encompassed by T is positive and larger. Tracings *E*, *F*, and *I* of Fig. 2 show a certain amount of auriculoventricular block, but in all the complexes chosen the rhythm was supraventricular.

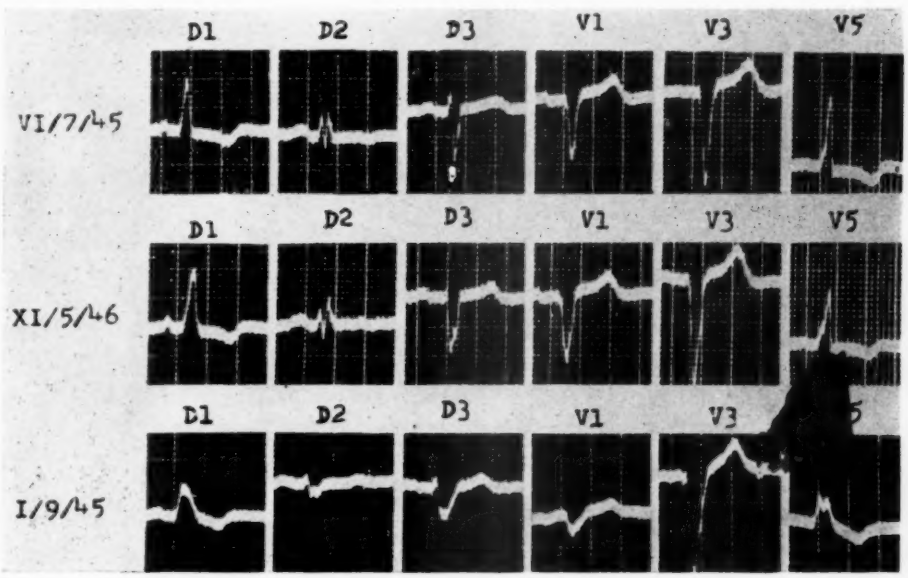

Fig. 3.*—Tracings from a patient with coronary artery disease. In the first two rows there is incomplete left BBB, which is recognized by the presence of an initial slurring in Lead V_5: in the third row, complete left BBB appeared.

The tracings with incomplete left BBB are recognized,[7] in man as well as in dog, by the presence of an initial slurring in the upstroke of those leads oriented to the free wall of the left ventricle. In Fig. 3 are shown three tracings from a patient with coronary artery disease. The first two with incomplete left BBB show the mentioned initial slurring in Lead V_5; afterwards, complete left BBB appeared. Later on we shall see that the presence of the slurring is more important than the absence of the Q wave[7] for the diagnosis of incomplete left BBB.

METHOD

The method used for this study was described in a previous paper.[15] Of the twenty-five patients studied by the method of arterial cardiac catheteriza-

*In this paper D1, D2, and D3 correspond to standard leads I, II, and III.

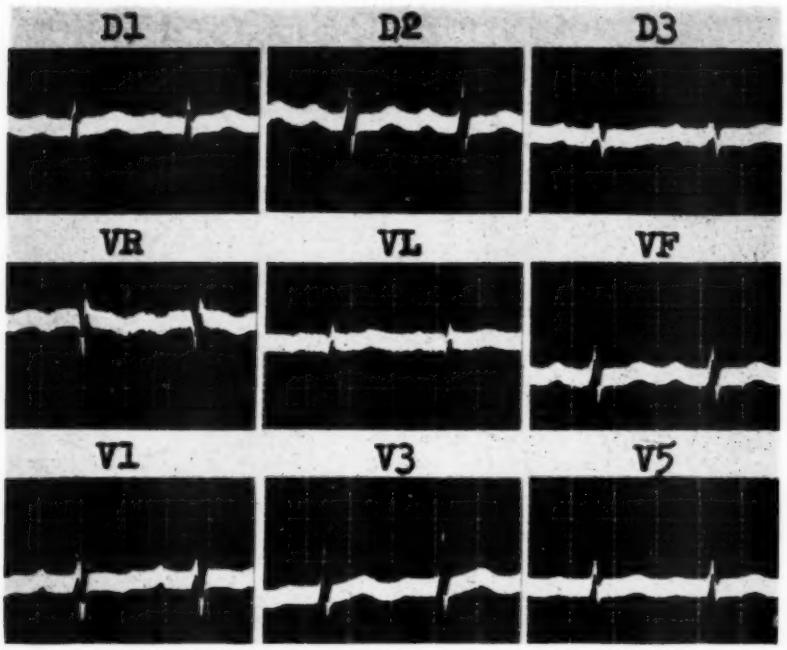

Fig. 4.—Electrocardiogram that could be considered within normal limits, taken from a patient with rheumatic heart disease.

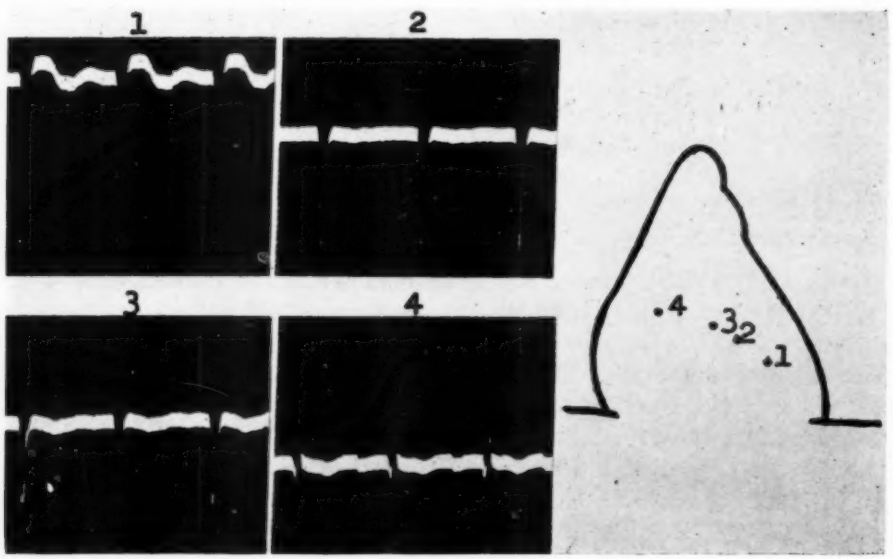

Fig. 5.—Tracings taken from the left ventricular cavity from the same patient as that of the electrocardiogram shown in Fig. 4. There is no evidence of incomplete left BBB.

tion, thirteen were concerned with the study of incomplete left BBB. The clinical diagnoses of the cases studied will be given with the discussion of each case.

Most tracings were taken with the Sanborn Cardiette. For some of them we used the Cambridge two-string machine or the Sanborn Poly-Viso. In all cases, we used electrocardiographic and fluoroscopic control, as described in a previous publication.[8]

RESULTS

A. *Cases Without Left Bundle Branch Block.*—From a group of ten patients in whom intracavitary potential was determined, four were chosen who were sufficiently characteristic to demonstrate the features of left intracavitary potential in the absence of left BBB.

In Fig. 4 is shown a practically normal electrocardiogram (with the exception of low voltage) from a patient with rheumatic heart disease. The left intraventricular tracings are shown in Fig. 5. The tracing taken at point *1* shows completely negative QRS complexes with elevation of the RS-T segment. This RS-T elevation was probably due to the pressure exercised by the exploring electrode. The P wave is positive. The tracings taken at points *2* and *3* are also of the QS type, with negative T wave and without elevation of the RS-T segment. In the third tracing just mentioned, the intrinsic deflection is inscribed rapidly, and there is practically no notching or slurring. That taken at point *4*, above the aortic valves, shows a morphology typically auricular: negative P and T waves and a rapid complex of the qR type.

In Fig. 6 is shown an electrocardiogram which is normal except for the initial straightness of the RS-T segment and the angularity of its junction with the T wave; that suggests the possibility of left ventricular hypertrophy. During the catheterization of this patient a tracing could be obtained at only one point in the left ventricular cavity (Fig. 6, point *1*), and a negative complex of the QS type with negative T wave was inscribed. The low voltage P wave is slightly diphasic. This patient has a rheumatic mitral stenosis and insufficiency.

Fig. 7 shows an electrocardiogram, taken from a patient with syphilitic aortitis and aortic insufficiency, very characteristic of left ventricular hypertrophy. In the standard leads it is seen that the voltage is very high, the index of Lewis being + 49 mm. The left precordial leads V_5 and V_6 are not oriented toward the thickest part of the ventricular wall and for that reason show transitional complexes. In V_L, the tracing is completely characteristic of the left ventricle, and the intrinsicoid deflection begins at 0.06 second. The U wave is typically negative in V_L and I.[12] Fig. 8, from the same patient, shows the tracing taken by catheterization. The tracings from the first four points in the left ventricular cavity show complexes of the QS type, with the T wave negative and peaked. At point *4* there is elevation of the RS-T segment which cannot be attributed to pressure of the electrode, since it continued to be registered at points higher up. The tracings from points *5*, *6*, *7*, *8*, and *9* were taken from the ascending aorta and are of the QS type with elevation of the RS-T segment. The P wave was identified with more difficulty than in the preceding tracings and is slightly

diphasic. The tracing taken at point *10*, near the aortic knob, is of the Qr type with negative T wave. The U wave is difficult to recognize in all of the ten points.

In Fig. 9, taken from a patient with hypertension, is shown another tracing suggestive of left ventricular hypertrophy. The index of Lewis is + 19 mm., and the T wave is negative in all the leads that reflect the potential of the left ventricle (I, V_L, and V_6). It is not possible to rule out anterolateral ischemia.

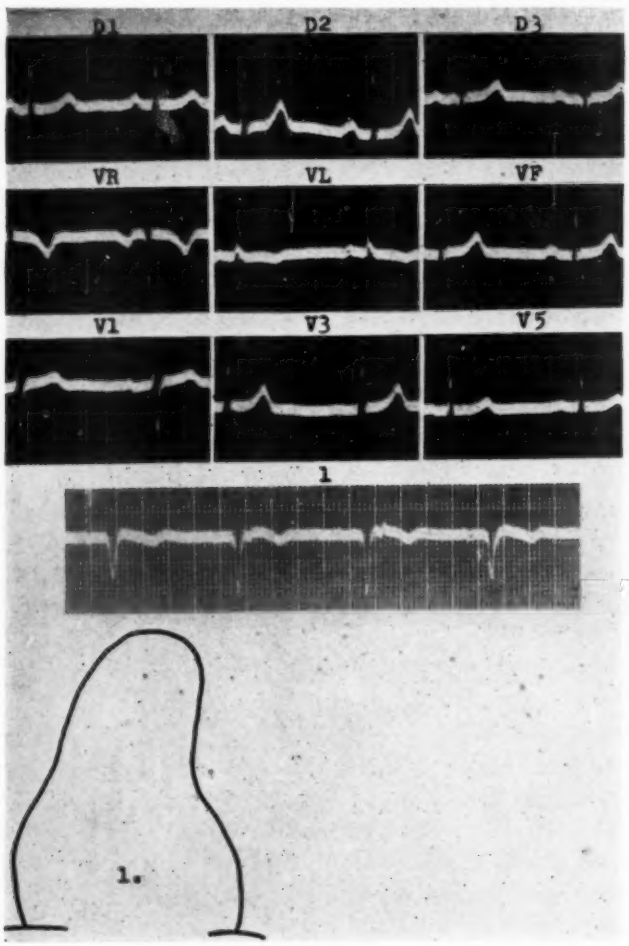

Fig. 6.—Tracings from a patient with rheumatic mitral stenosis and insufficiency. The usual electrocardiogram shows very slight change in the P wave of Lead II. In the left intracavitary tracing, the complex is entirely negative, and there is no evidence of incomplete left BBB.

In the standard leads, the P wave shows notches and slurring. The intraventricular tracings are shown in Fig. 10. The tracing taken at point *1* shows a wholly negative complex with elevation of RS-T; there are artifacts which resemble the P wave. The tracing from point *2* is of the QS type with a positive

T wave. At the same point a ventricular extrasystole is inscribed. That from point *3* is similar, but the T wave is less positive. In all of them there was noted a rapid inscription of the intrinsic deflection. The tracing from point *4* was taken above the aortic valves and is of the Qr type with negative T wave and diphasic P wave.

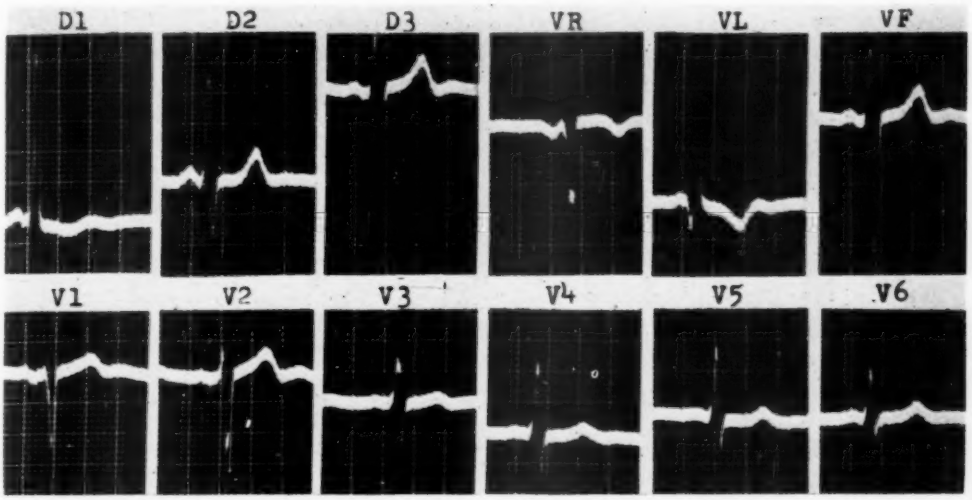

Fig. 7.—Tracings taken from a patient with left ventricular hypertrophy. The clinical diagnosis was: syphilitic aortitis with aortic insufficiency. Index of Lewis + 49 mm.

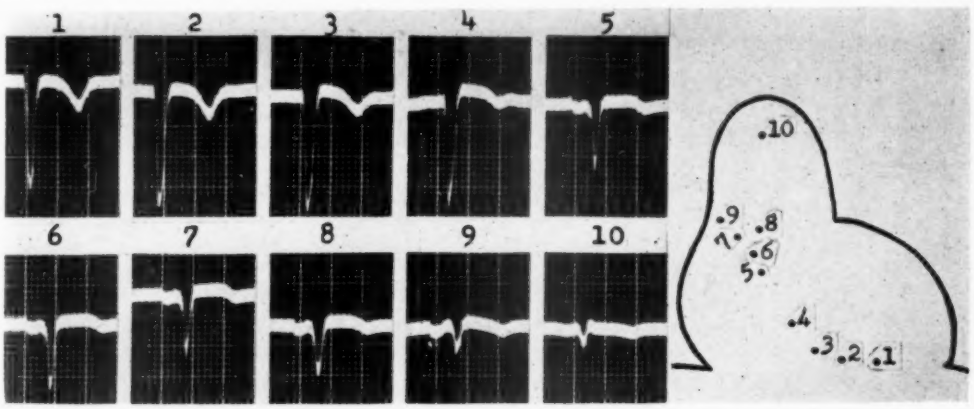

Fig. 8. Tracings taken from the left ventricular cavity from the same patient as Fig. 7. The first four tracings were taken inside the left ventricular cavity, and the rest were taken from the aorta above the aortic valves. There is no evidence of left BBB.

In the four patients just cited, there was no initial positivity in the cavity of the left ventricle, and for that reason we cannot speak of incomplete left BBB. Nevertheless, we shall see later on that slight grades of left BBB can be recognized only by taking bipolar leads across the interventricular septum.

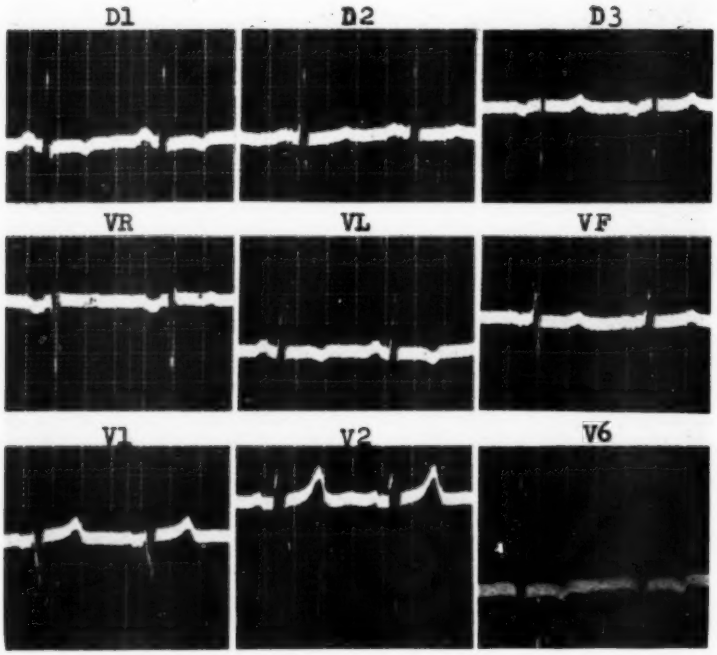

Fig. 9.—Tracing suggestive of left ventricular hypertrophy, taken from a patient with hypertension.

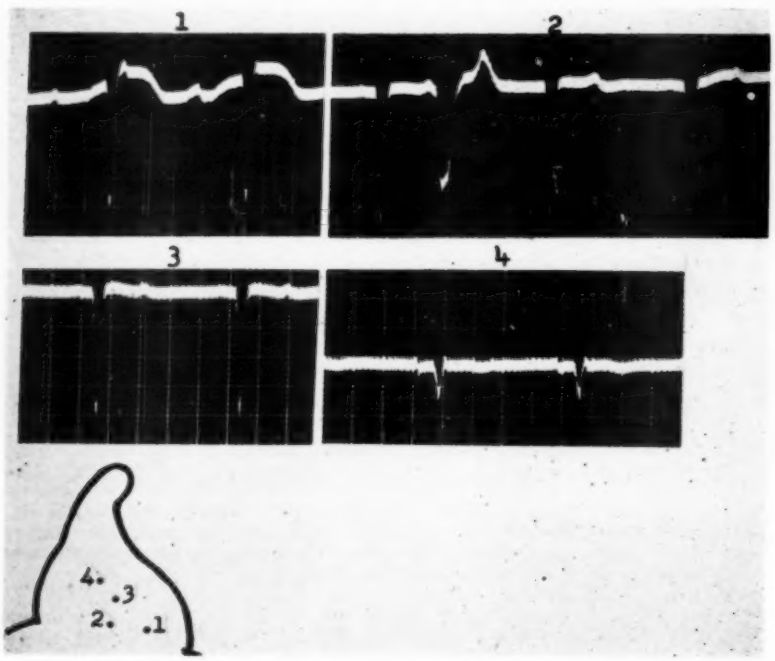

Fig. 10. Intraventricular tracings taken from the same patient as in Fig. 9. The first three tracings were taken from the left ventricular cavity and the fourth from the aorta above the aortic valves. There is no evidence of left BBB.

Notwithstanding that the morphology of the tracings taken above the aortic valves is not the same as that of the intracavitary tracings, we would like to point out that in none of the ten patients of this group was there initial positivity in the rapid ventricular complex taken from that site. In those patients with incomplete left BBB this initial positive deflection is present.

B. *Cases With Left Bundle Branch Block.*—In Fig. 11, taken from a patient with aortic stenosis and insufficiency, probably rheumatic, is shown a tracing strongly suggestive of left ventricular hypertrophy. In this tracing there is left axis deviation, and the index of Lewis is + 27 mm. The intrinsicoid deflection in V_5 begins its inscription at 0.05 second. Notwithstanding that there is a Q wave in Leads I and V_5, there is slurring of the beginning of the ascending limb of R that suggests the possibility of incomplete block. In the intracavitary tracing of this patient registered near the apex of the heart, a tracing of the RS type was obtained (Fig. 12, point *1*), with a positive T wave. This type of tracing is very characteristic of left BBB and is very similar to that found in the dog after the left branch of the bundle of His has been cut. At point *2* of Fig. 12, above the aortic valves, the tracing is of the rS type with a positive T wave, in contrast to the tracing in patients without BBB in which no initial positivity was found at this point. This case is very demonstrative, in that it shows that it is possible to have incomplete left BBB with a QRS duration of less than 0.10 second and in the presence of Q waves in I and V_5. It is worth pointing out, too, that the U wave is negative and easily recognizable in I and V_5, although it is not found in the intracavitary tracings. This makes it difficult to accept the hypothesis that the U wave is a consequence of septal repolarization, as has been suggested recently.[11,12] The T wave is negative in the left precordial leads and positive in the intraventricular tracing, which suggests that in this particular case there are clear differences in the repolarization of the subendocardial and subepicardial muscle of the free wall of the left ventricle. It is convenient to emphasize once again the importance of the slurring of the ascending limb of R, since it is an important point in the diagnosis of incomplete left BBB. The slurring, as we have held previously, is very similar to that obtained in the dog when the left bundle branch is tapped. There remains to be explained the presence of a Q wave in I and V_5, since in this particular case septal activation is developed from right to left, or in a manner opposite to the normal. We believe that these two leads, I and V_5, are not well oriented toward the left ventricle, and that if in the majority of cases V_7 and V_8 are taken, or if tracings are taken at lower levels, the Q wave will disappear. In many cases the exploring electrode (especially when V_L is used) is oriented toward the left auricle, and it must be remembered that in the dog in that cavity the complex is of the qR type (the R is slurred) after the left bundle branch has been cut.[7] In this way it is easy to understand the presence of a Q wave in left block in the absence of a myocardial infarct.

In Fig. 13, taken from a patient with aortic insufficiency, probably of syphilitic origin, is shown another tracing characteristic of left ventricular hypertrophy. There is no left axis deviation, but the T waves are quite characteristic, and the beginning of the intrinsicoid deflection in V_5 is inscribed at 0.05 second. There is no Q wave in I, and in V_5 it is very small, a fact that taken by itself

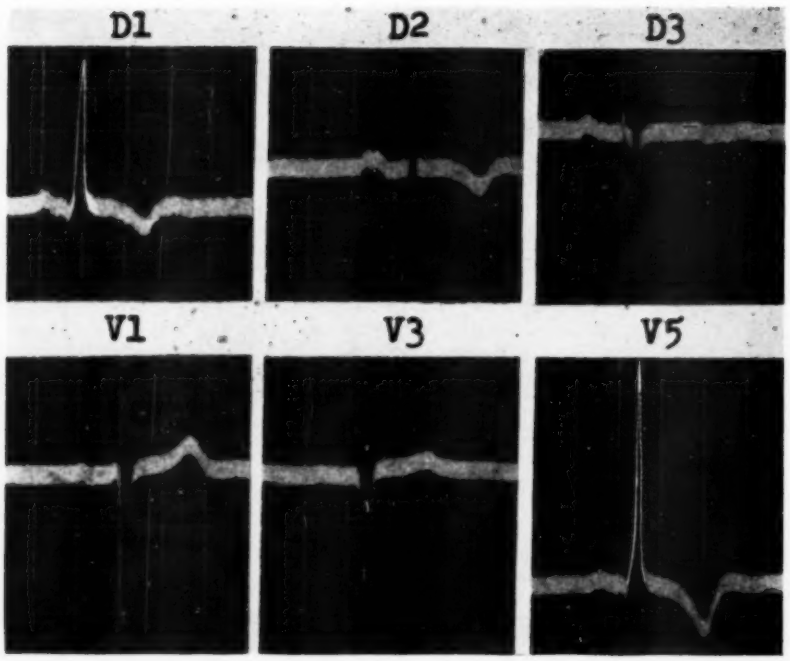

Fig. 11.—Tracing strongly suggestive of left ventricular hypertrophy, taken from a patient with aortic stenosis and insufficiency, probably rheumatic. Notwithstanding the presence of a Q wave in Lead I (D1) and V_5, there is slurring of the beginning of the ascending limb of R, which suggests incomplete left BBB. This tracing was retouched in I and V_5 (see Fig. 12).

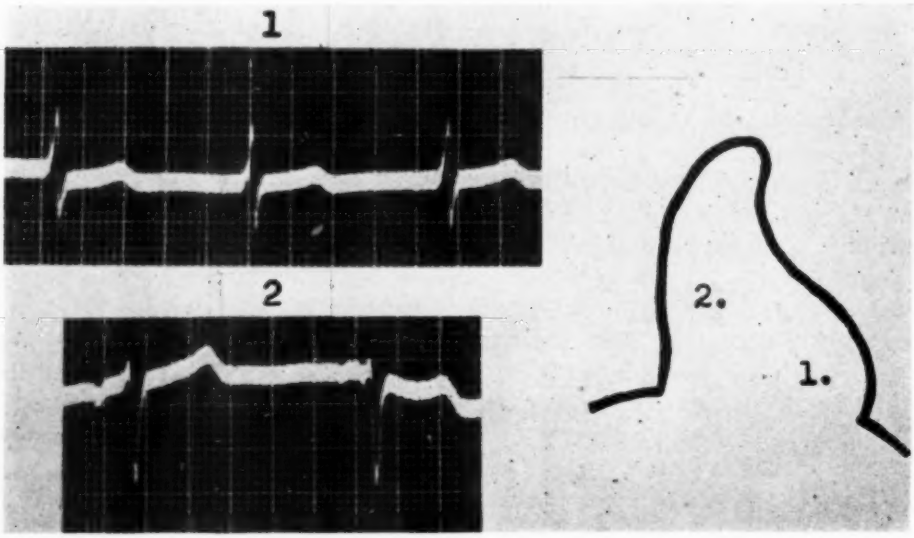

Fig. 12.—Left intracavitary and aortic tracings from the same patient as in Fig. 11. Tracing *1* is of the RS type and was taken from inside the ventricle. It is very characteristic of left BBB and very similar to those found in the dog after the left bundle branch was cut. Tracing *2*, taken above the aortic valves, is of the rS type, also characteristic of left BBB.

would lead one to think of the possibility of incomplete left BBB, in spite of the fact that there is practically no initial slurring of R. In the intraventricular tracings (Fig. 14) at point *1*, near the apex, a complex of the rS type with negative T and U waves was obtained. In the intracavitary R wave there is marked notching, as if there were a tendency to the inscription of two positivities. The tracing taken above the aortic valves shows a very small initial positivity, and the P and T waves are negative (Fig. 14, point *3*). This example is also very

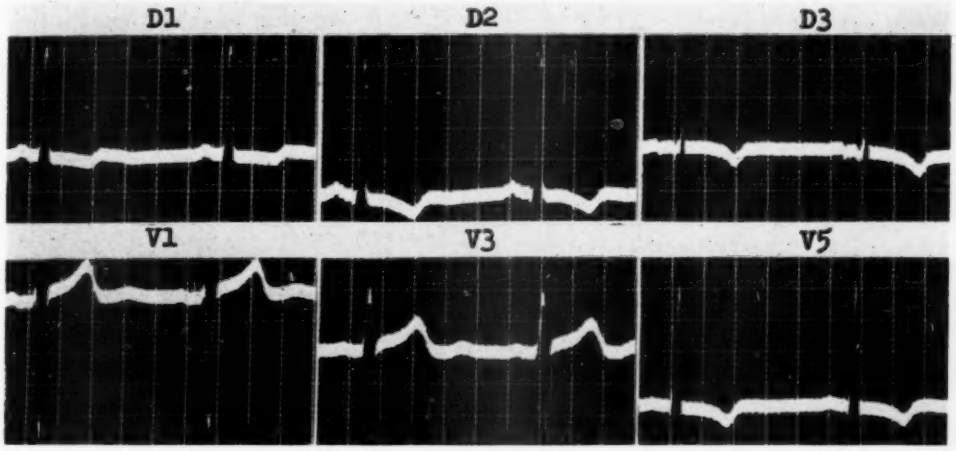

Fig. 13.—Tracings characteristic of left ventricular hypertrophy, taken from a patient with aortic insufficiency, probably syphilitic. Note the absence of Q in Lead I (D1) and smallness of Q in V_5, which taken alone would lead one to suspect incomplete left BBB (see Fig. 14).

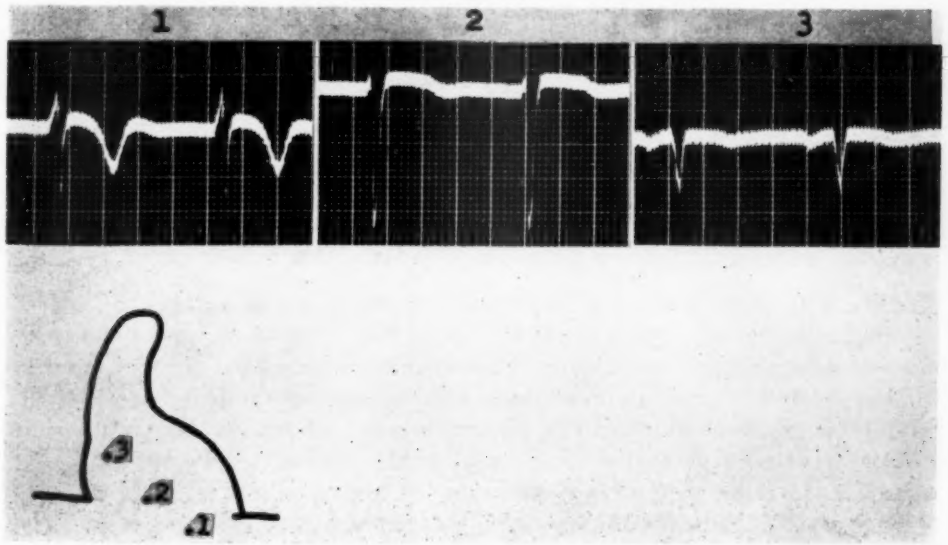

Fig. 14.—Intracavitary and intra-aortic tracings from the same patient as in Fig. 13. Tracings *1* and *2*, taken inside the left ventricular cavity, show an initial upright deflection, quite characteristic of left BBB. Tracing *3*, taken from above the aortic valves, shows no initial positivity.

demonstrative, since in spite of a QRS duration of only 0.08 second, there is undoubtedly a certain degree of left block.

Fig. 15 shows a tracing that could well correspond to incomplete BBB, or to the syndrome of Wolff-Parkinson-White. In I, V_1, and various precordial leads, there is an initial slurring of the ascending limb of R that is suggestive of Wolff-Parkinson-White syndrome. Nevertheless, the P-R interval is 0.16 second in II, and clinically there was nothing to suggest the Wolff-Parkinson-White syndrome. We believe that many cases diagnosed as Wolff-Parkinson-White syndrome actually are incomplete left BBB, and it is pertinent to cite the

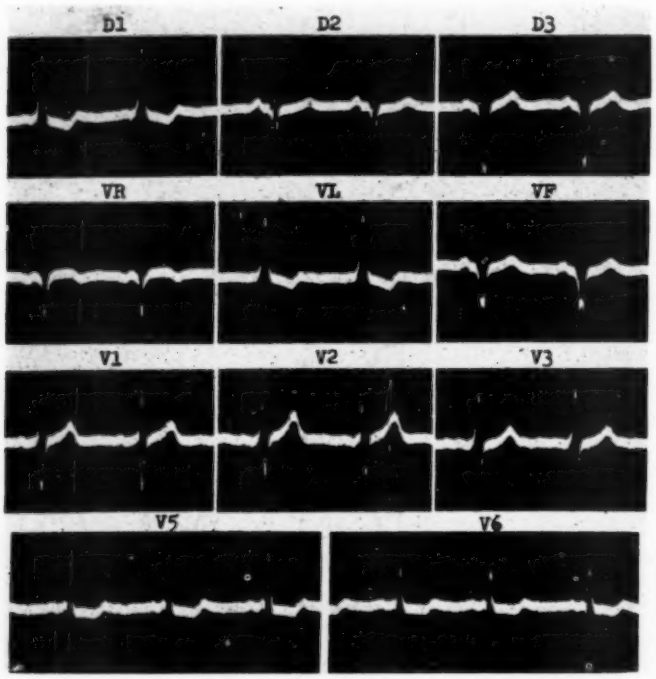

Fig. 15.—Tracing that could correspond to either left BBB or Wolff-Parkinson-White syndrome. The P-R interval is 0.16 second in Lead II (D2) (see Fig. 16).

patient with Wolff-Parkinson-White syndrome in whom Mahaim[13] studied histologically the left branch of the bundle of His, demonstrating inflammatory lesions. Moreover, the same slurring appears in the dog's tracing with the production of left BBB, and in man identical slurring is found in tracings that later may go on to complete left BBB (Fig. 3); and in those cases there is no possibility of confusion with Wolff-Parkinson-White syndrome. In Leads V_5 and V_6 of Fig. 15 there are two positivities, showing a tendency to an M complex. The QS complex of Leads III and V_F is seen frequently in BBB and is not indicative of infarction. The alterations of T and RS-T appear to be secondary and therefore oppose the areas englobed by QRS. The intracavitary study (Fig. 16) shows near the apex of the left ventricle (point *1*) a complex of the rS

type with negative T. The initial positivity is indicative of block and, in accordance with studies done in animals, corresponds to septal activation from right to left. The tracing taken above the aortic valves is very similar to the intracavitary tracing. A bipolar tracing across the septum was taken from point *1*, located in the left ventricle, to point *3* in the right ventricle (Fig. 16), the positive electrode being in the left ventricle. The deflection thus obtained is essentially positive (Fig. 16, inferior curve) and indicates that the septal activation is from right to left, that is, from point *3* of the right ventricle to point *1* of the left ventricle.

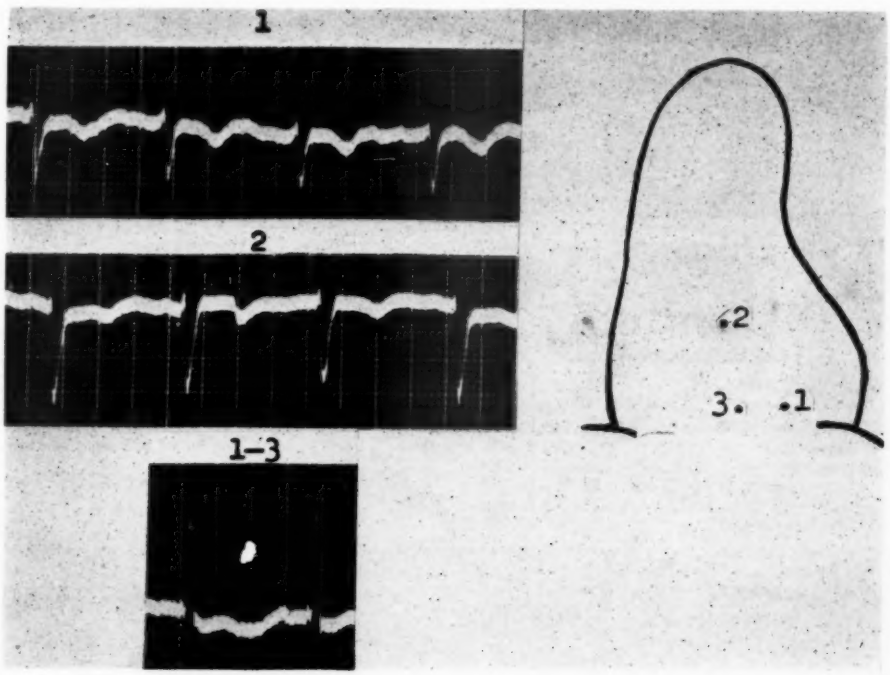

Fig. 16.—Intracavitary studies (right and left ventricles) of the same patient as shown in Fig. 15. Tracing *1*, taken from the left ventricle near the apex, shows a complex of the RS type, which indicates septal activation from right to left. Tracing *2*, taken from above the aortic valves, is similar. A bipolar tracing across the septum was taken from point *1* in the left ventricle to point *3* in the right ventricle, the positive electrode being in the left ventricle. The deflection obtained is essentially positive, indicating septal activation from right to left.

In Fig. 17 is shown another case which quite possibly is incomplete left BBB instead of Wolff-Parkinson-White syndrome. It was taken from a patient with aortic insufficiency and mitral insufficiency and stenosis, who gave no history of bouts of tachycardia. The QRS duration is from 0.14 to 0.15 second and the P-R interval in Lead II is 0.14 second.

In the left intracavitary study (Fig. 18, points *1*, *2*, and *3*) there was registered an initial positivity that corresponds to the activation of the septum from right to left. We can refer the negativity that follows the initial intracavitary positivity to the free wall of the left ventricle, and it will be, therefore,

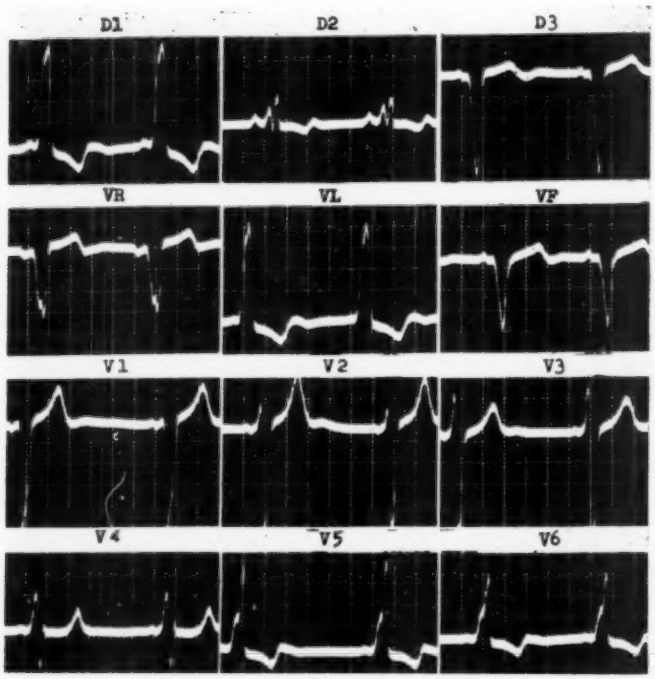

Fig. 17.—Showing another case which could correspond to either incomplete left BBB or Wolff-Parkinson-White syndrome. The P-R interval in Lead II is 0.14 second. The clinical diagnosis was aortic insufficiency and mitral insufficiency and stenosis. There was no history of episodes of tachycardia (see Fig. 18).

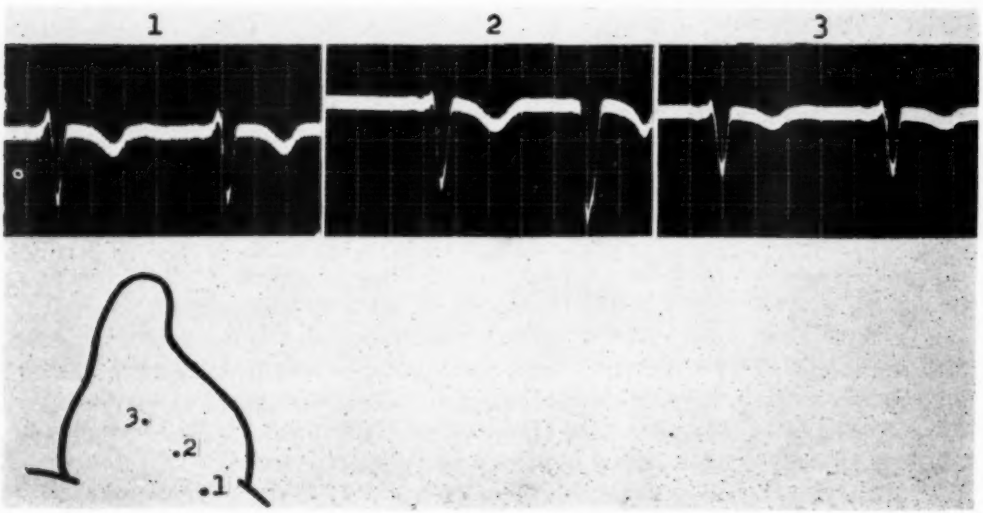

Fig. 18.—Intracavitary and intra-aortic studies from the same patient as in Fig. 17. Tracings *1* and *2*, taken from inside the left cavity, show initial upright deflection, which indicates septal activation from right to left.

synchronous with the termination of R in the left precordial tracings. The T wave is negative in both the intracavitary and extracavitary leads, which shows the importance that septal repolarization has in this case.

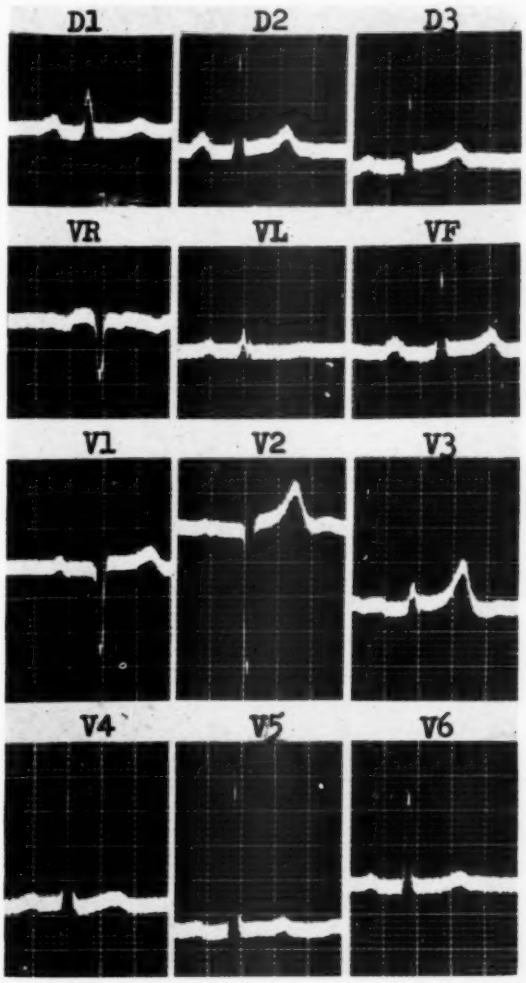

Fig. 19.—Tracing from a patient with mitral stenosis and insufficiency. There is nothing to suggest the presence of left BBB except the absence of Q in Lead I and the left precordial leads.

The case shown in Fig. 19, from a patient with mitral stenosis and insufficiency and aortic insufficiency, is even more interesting. There is nothing to suggest the presence of incomplete left BBB except the absence of Q in Lead I and the left precordial leads, and it has nothing to distinguish it from the tracings of many rheumatic patients. The intracavitary study (Fig. 20) shows a completely negative complex at point *1* in the left ventricle, of the QS type with slurring of the descending limb and a positive T wave. Since this slurring was suspicious of block, the right ventricle was also catheterized (Fig. 21) and the unipolar

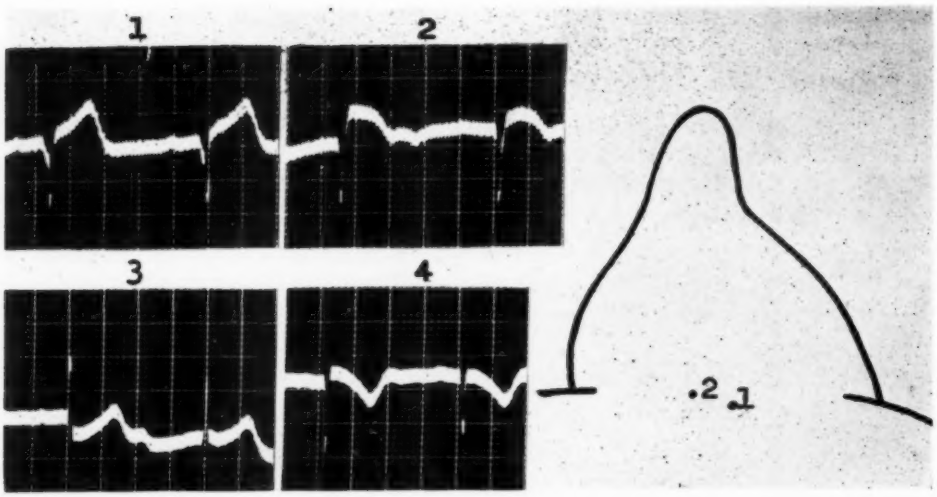

Fig. 20.—Intracavitary studies from the patient in Fig. 19. At point *1* in the left ventricle a completely negative complex of the QS type with slurring of the descending limb was recorded. Since this slurring caused us to suspect block, the right ventricle was also catheterized, and the unipolar tracing recovered from that ventricle (point *2*) also was of the QS type. A bipolar tracing was then taken from point *1* to point *2*, left ventricle to right ventricle, which is seen in tracing *3*, which shows a completely positive complex, indicating that the septal activation at the level of the electrodes is from right to left. The tracing in *4* was taken in the same manner except that the polarity was reversed.

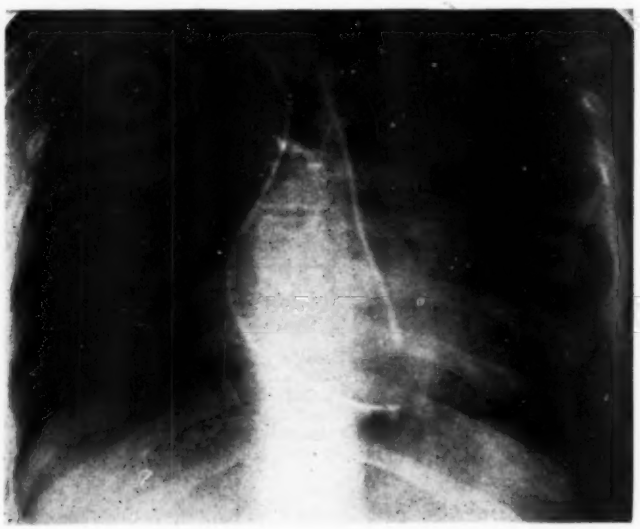

Fig. 21.—Showing a roentgenogram with the catheters in both ventricles, as used in obtaining the tracings of Fig. 20.

tracing recovered from that ventricle is of the QS type (Fig. 20, point *2*), although in the first complex there is a late R and elevation of the RS-T segment caused by the pressure of the exploring electrode. Up to this point we were dealing with a patient with wholly negative complexes in both ventricular cavities;

that, according to the principles set forth previously, would correspond to a minor grade of left block. In order to demonstrate this point, we took a bipolar tracing from point *1* to point *2*, similar to that done in one of the previous cases. It was possible to show (Fig. 20, tracing *3*) a completely positive complex, which indicates that the septal activation at this level is realized from right to left; this means that there is a certain degree of left BBB. In the curve shown at point *4*, the polarity was reversed, and the tracing became completely negative. The T wave of considerable magnitude in this bipolar tracing serves to point out the different degree of repolarization on the two septal surfaces.

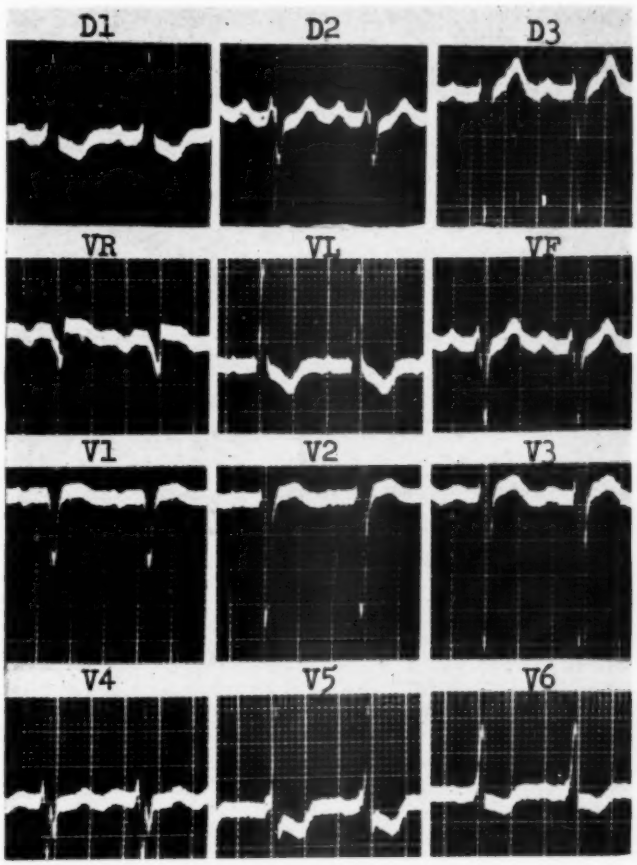

Fig. 22.—Tracing from a patient with hypertension. The initial slurring, very marked in the leads that reflect the potential of the left ventricle, especially Leads I and V_5, is strongly suggestive of incomplete left BBB.

C. *Cases With Probable Left Bundle Branch Block.*—The tracing of Fig. 22 is strongly suggestive of incomplete left BBB because of the presence of an initial slurring, very marked, in the leads that reflect the potential of the left ventricle, especially I and V_5. The patient from whom the tracing was taken was hypertensive. In the intracavitary study (Fig. 23, upper tracing) the complex is entirely negative, but in the descending limb a sharp notch synchronous with the

slurring of the ascending limb of V_6 is seen (lower tracing of Fig. 23). This case is very similar to that shown in Fig. 20, which was proved, by a bipolar transeptal tracing, to be incomplete block.

A case very similar to the previous one is shown in Fig. 24. The initial slurring of the ascending limb of R in Leads I, V_L, and V_5 is strongly suggestive of incomplete left BBB. The duration of QRS is 0.11 second. There is no Q wave in any of the leads that reflect the potential of the left ventricle. In addition, there is first degree atrioventricular block, and the alterations of T appear to be secondary to those of QRS. The clinical diagnosis was syphilitic aortic insufficiency. Intracavitary studies of the left ventricle (Fig. 25, points *3*, *4*, and *5*) show entirely negative complexes of the QS type, and at point *5* they show elevation of RS-T and a negative T wave. At point *3*, there is initial slurring in the descending limb of QS very similar to that of the preceding case and that observed in Fig. 20, where the existence of block was demonstrated.

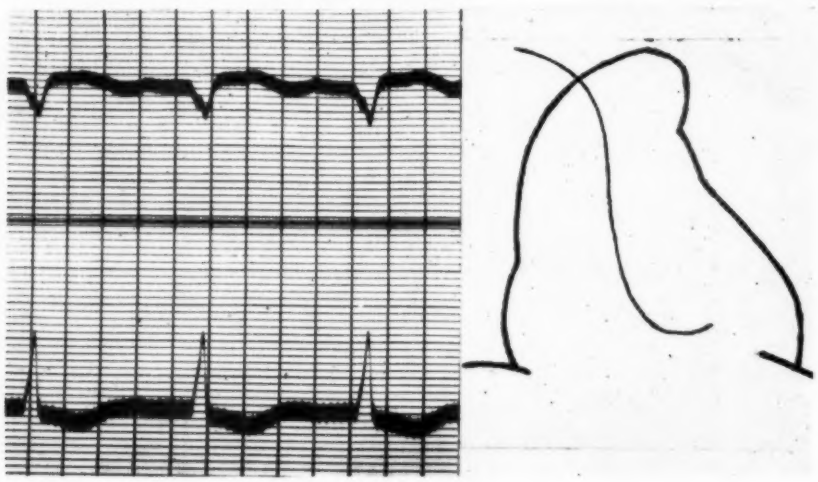

Fig. 23.—Intracavitary studies of the same patient as in Fig. 22. The complex recorded in the left ventricle (upper tracing) is of the QS type without positive deflections, but in the descending limb there is a sharp notch synchronous with the slurring of the ascending limb of V_6, shown in the lower tracing of the same figure. This case is very similar to that shown by bipolar transeptal tracings to represent incomplete left BBB.

In tracing *3* there is a ventricular extrasystole. Before the electrode was introduced into the ventricular cavity, the catheter veered to the right, probably entering the right coronary artery. The morphology of P at point *1* (Fig. 25) suggests the proximity of auricular musculature (auriculoventricular groove?). The complex is of the QS type, and the slurring is very marked. At point *2* near the aortic valves there is an initial positivity of the ventricular complex, which suggests block.

In two other cases suggestive of incomplete left BBB (Figs. 26, 27, and 28) the electrode passed only as far as the aortic valves, and in both an initial positivity was registered in the ventricular complex (Figs. 26 and 28), a finding that reinforces, as we said before, the possibility of incomplete left BBB.

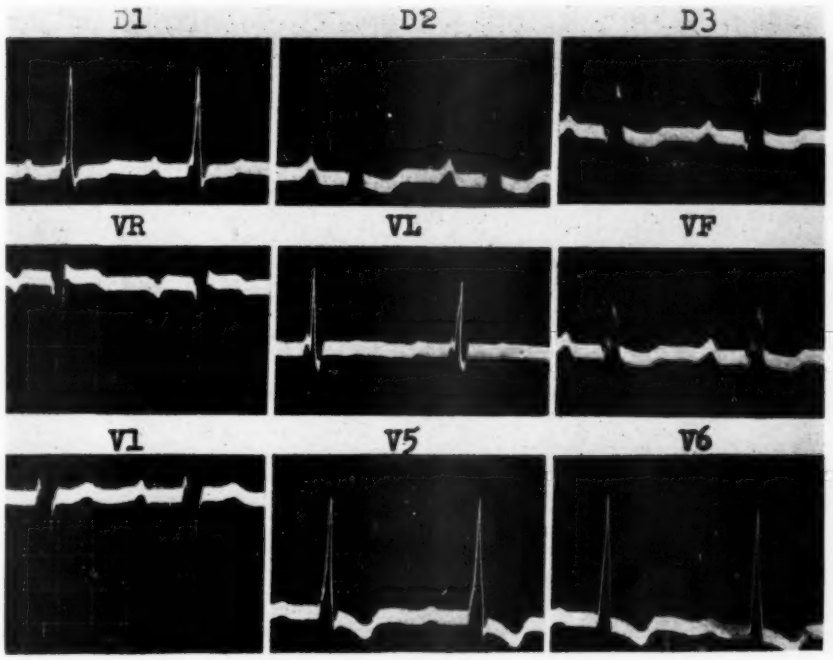

Fig. 24.—Tracing showing an initial slurring in the ascending limb of R in Leads I, V_L, and V_5, which is strongly suggestive of incomplete left BBB. The clinical diagnosis was syphilitic aortic insufficiency. This tracing was retouched in Leads I, V_L, V_5, and V_6.

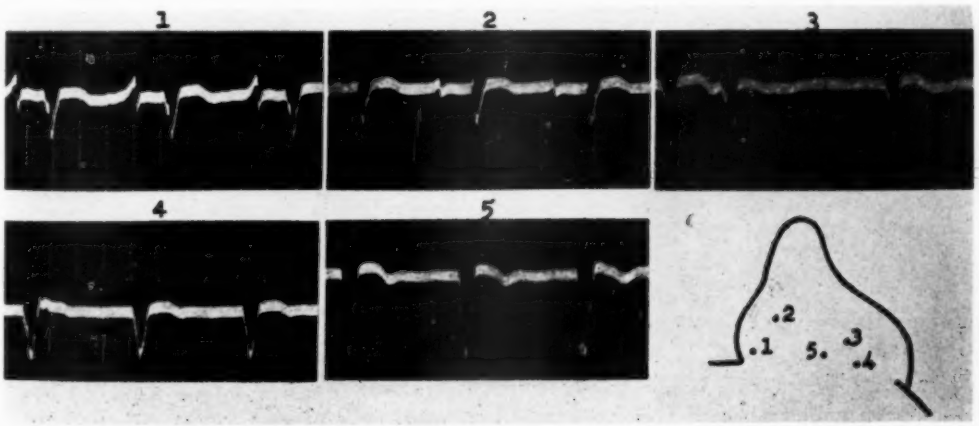

Fig. 25.—Intracavitary studies of the same patient as in Fig. 24. The tracings taken at points *3*, *4*, and *5* in the left ventricle are completely negative and of the QS type. At point *3*, there is an initial slurring of the descending limb of QS, very similar to that observed in Fig. 20. For points *1* and *2*, see the description in the text.

FINAL COMMENTS

If our reasoning is correct, a great many cases considered as characteristic of left ventricular hypertrophy are in reality incomplete left BBB, although we are by no means implying that there is not coexistent hypertrophy as well. Moreover, the hypertrophy could well be the cause of the appearance of the block. In right BBB this is even more likely, and we feel that tracings showing right ventricular hypertrophy without some degree of right BBB are indeed exceptional. There is another datum that substantiates this opinion, and that

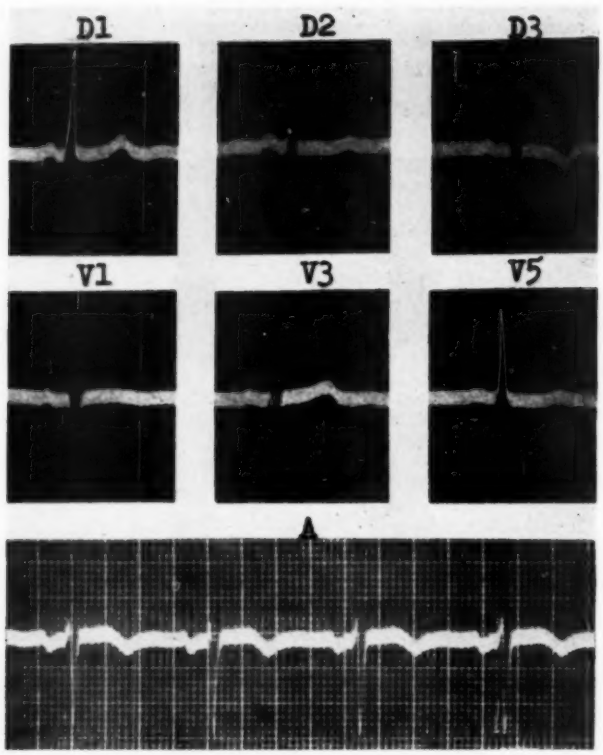

Fig. 26.—In this patient, the absence of Q in Leads I and V_5 and the initial slurring of the ascending limb of R in V_5 suggested incomplete left BBB. In tracing *A* of the same figure is shown the complex with initial positivity taken from a point above the aortic valves, which is as far as the catheter passed. As has been pointed out before, this is extremely suggestive of incomplete left BBB. This tracing was retouched in Leads I and V_5.

is that in post-mortem study it is very common to find right ventricular dilatation without hypertrophy, at times with very thin ventricular walls, in the presence of complexes of the types RS, qR, and QR (in the absence of infarction) in the right precordial leads. Moreover, the following is even more credible in the light of the extreme lability of the right branch of the bundle of His. It would appear, therefore, that ventricular hypertrophy without block is less frequent than ordinarily considered, and that block, with or without hypertrophy, is far more

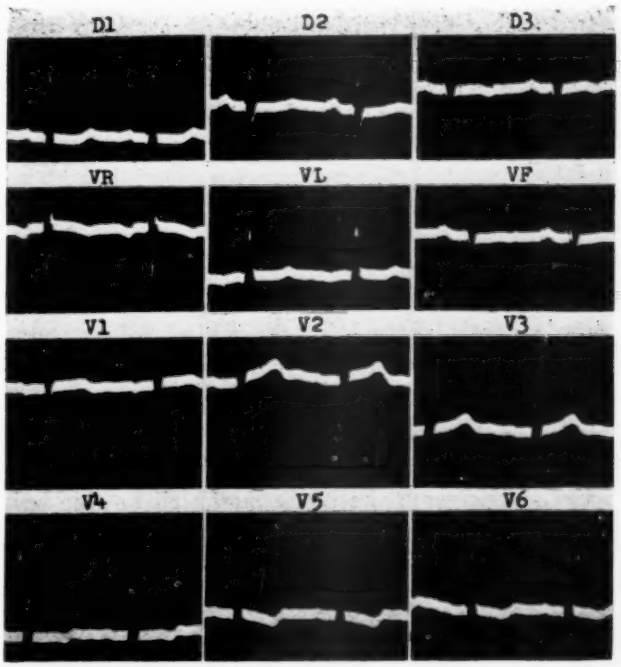

Fig. 27.—Case showing left ventricular hypertrophy with nothing to suggest left BBB.

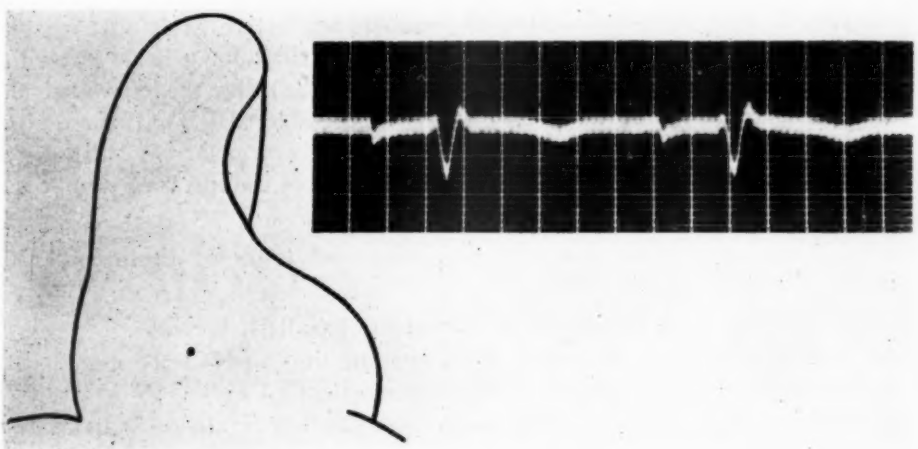

Fig. 28.—Tracing from the same patient as in Fig. 27, taken from a point above the aortic valves, which is as far as the catheter passed. There is an initial positivity which could correspond to a slight degree of left BBB.

frequent than heretofore thought to be. It is obvious that to be absolutely certain of this it will be necessary to do catheterization of both ventricles in a great many patients.

Nevertheless, up to this point we believe that the term incomplete left BBB should be applied only to those tracings in which the morphology suggests the existence of an initial positivity in the cavity of the left ventricle. This is recognized by the initial slurring of the ascending limb of R that we have mentioned so much. Tracings with this morphology can give one a definite orientation in the clinical diagnosis, and we have encountered them in hypertension, coronary heart disease, and syphilitic aortitis with aortic insufficiency. Very frequently in aortic insufficiency, it is difficult to determine whether the etiology is syphilitic or rheumatic, and it is worth mentioning that we have not encountered this type of tracing in rheumatic aortic insufficiency. This refers to insufficiency without stenosis, since in stenosis block of any grade is frequent. Calcific aortic stenosis, alone or associated with other valvulopathies, also is frequently complicated by left BBB.

We will not discuss the possible etiologies of left BBB, since they are a much debated question, but it is worth mentioning that in those patients with syphilitic aortitis and aortic insufficiency, the block may well be due to the descending septal myocarditis described by Costero and collaborators,[14] and that on various occasions we have been able to make such a diagnosis because of the presence of an initial slurring of R.

CONCLUSIONS

1. The diagnosis of BBB can be made in the presence of QRS complexes with durations of less than 0.10 second.

2. The study of left intraventricular potential in the human heart has demonstrated that a large number of tracings suggestive of left ventricular hypertrophy are actually incomplete left BBB. In the human heart as well as in the dog's heart, the rapid ventricular complex (QRS) inside the left ventricular cavity is of the QS type in the absence of any degree of left BBB. If there exists some degree of left BBB, the tracing inside the left ventricular cavity shows an initial positivity which corresponds to the activation of the intraventricular septum from right to left.

3. It is possible that some tracings diagnosed as the syndrome of Wolff-Parkinson-White are left BBB.

4. Essentially, the diagnosis of incomplete left BBB is made by the presence of slurring in the beginning of the ascending limb of R in those leads that reflect the potential of the left ventricle, most frequently Leads I, V_L, V_5, and V_6. The absence of Q in the same leads also suggests such a diagnosis, but the block can exist even in the presence of a Q wave in these leads. The duration of QRS is not of importance in making the diagnosis.

5. In some patients it is necessary to catheterize both ventricles and register a bipolar lead across the septum in order to make the diagnosis.

6. In the majority of patients the diagnosis of incomplete left BBB can be established by taking tracings with the electrode above the aortic valves without introducing the catheter into the left ventricular cavity.

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THE SUPERIORITY OF THE WILSON LEADS AND THE VALUE OF UNIPOLAR LIMB AND PRECORDIAL DERIVATIONS IN CLINICAL ELECTROCARDIOGRAPHY

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FRANK N. WILSON presented in discussion the mathematical background and basis of his work on electrical potentials in the human heart and pointed out the value of unipolar chest and limb leads at the First Inter-American Congress of Cardiology held at the inauguration of the Instituto Nacional de Cardiologia de México. A sharp attack on the validity of the Wilson theory and claims of alleged superiority of other precordial systems were countered by the senior author who concluded with the suggestion that all of the methods be put to a practical test. The test was to consist of the simultaneous taking of the usual limb and unipolar limb leads and the four common types of chest leads in 200 patients for correlation studies. The changes in the V or Wilson leads[1] taken from chest positions 1 to 6 and the findings in the CR, CF, and CL leads from the same chest positions were to be compared. This has recently been done by us, and the analysis of the data serves as the basis of this paper.

Somewhat similar, but less extensive and less complete, studies have been made with conflicting and inconclusive results. Wallace and Grossman,[2] in 1946, concluded that V or Wilson leads offered no advantage over the CF leads. Dolgin, Grau, and Katz,[3] from the same laboratory in 1949, reported a study in which a comparison was made of the four types of precordial leads. They concluded that although in the majority of cases there was no significant difference, in approximately 5 per cent there were undesirable variations shown chiefly in the CF leads. The substitution of the V or Wilson leads could eliminate these effects of extremity potential on the precordial electrocardiogram. The Philadelphia group, particularly Wolferth and Bellet,[4] have insisted that the CR leads are the best. Hoyos and Tomayo[5] found no important variation among the various precordial leads. They felt that CR leads were as reliable as the V leads, but that both showed less variation than the CF leads.

However, as early as 1942, Hecht,[6] using an extremity for the indifferent electrode, reported a considerable effect on the precordial leads. This was a result of the potential variations of the left arm in CL leads and the left leg in CF leads. These variations were due to alterations in the mean electrical position of the heart. He stated that although the distortion in the CR leads is not appreciably less than that in CL and CF leads, it is more uniform in

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magnitude and duration. Hull and associates[7] called attention to false abnormalities occurring in a few cases in the CF leads, leading at times to T-wave inversions. Leatham[8] in a study of CF, CR, and V leads in healthy adults discarded the CF leads after 50 tracings because of their variability. After 50 additional tracings, he concluded that in the normal individual CR and V leads have little practical advantage over each other. However, his study did not include patients with pathologic hearts. Myers and co-workers[9] have correlated exhaustively the findings in V leads with post-mortem studies in myocardial infarction, and in that manner they have demonstrated their value in depicting and localizing cardiac pathologic conditions.

Since the potential of the central terminal varies less than 3 to 3.5 mm. (Wilson and associates[10]), from a theoretical standpoint it would certainly be the most reliable as the indifferent electrode. However, in spite of widespread use of multiple precordial leads, there still is not complete agreement as to the most desirable indifferent electrode, even by the Committee on Electrocardiography of the American Heart Association.[11]

Electrocardiographic analyses, like radiologic findings, are to be interpreted in the light of history, physical examination, laboratory findings, and the clinical diagnosis. Prognostications can be made only with complete consideration of the patient as a whole, his economic status, and environment. Overenthusiasm among the young electrocardiologists leads to a tendency to overemphasize minor electrocardiographic changes and to err in reading too much into the tracings. The determination of the significance of an abnormality of the electrocardiogram in the diagnosis and treatment of a patient requires the skill and broad experience of an internist who is also a cardiologist.

The analysis of the electrocardiogram, the purely physical study, consists of identifying the P, Q, R, S, and T waves; the character, direction, and potentials of each; the rhythm and rate; the sequence and the duration of the intervals P-Q, QRS, and Q-T; the average electrical axis; and the vectors. This is the analytical study of the electrocardiogram.

The interpretation is a much more important and complicated diagnostic process. The significance of any finding depends upon directly associated symptoms and signs in the clinical study of the patient. The diagnosis of heart disease should be made only on the history of the typical cardiac pain and/or the finding of reliable physical signs of damage to the aorta, valves, or myocardium. Neither the complete diagnosis nor prognosis of heart disease can be made from the electrocardiogram without the clinical facts. Such should not be attempted. If it is attempted, errors will result, and a valuable method will be in disrepute.

Certain electrocardiographic abnormalities have been well established as occurring almost invariably with various types of myocardial damage. Characteristic patterns are to be found in the arrhythmias, myocardial infarction, right or left ventricular hypertrophy, pericarditis, and bundle branch block, but these should be interpreted in relation to the clinical findings. At its best, electrocardiography can be considered as only a valuable adjunct and supplement to a detailed clinical study of the patient. For example, although the

finding of bundle branch block usually indicates myocardial damage, such patients, particularly with right bundle branch block, have been known to live out their full life span without symptoms and to die from other causes.

THE CHEST OR PRECORDIAL LEADS

The value of chest leads in electrocardiography has been well established, and the importance of multiple leads with the exploring electrode has been demonstrated by various authors.[12] Precordial leads are designated as V, CR, CF, and CL, depending upon whether the indifferent electrode is the central terminal of Wilson, the right arm, the left leg, or the left arm. We believe that the numeral designating the position of the exploring electrode on the chest should follow the C, and not the R, F, or L that indicates the position of the indifferent or distant electrode. The usual positions for placement of the precordial electrode are: 1—the fourth intercostal space at the right margin of the sternum; 2—the fourth intercostal space to the left of the sternum; 3—midway on a straight line between positions 2 and 4; 4—mid-clavicular line in the fifth intercostal space; 5—left anterior axillary line at the same level; and 6—midaxillary line. Occasionally, the additional following leads may be taken in a straight line from 5 and 6: 7—posterior axillary line; 8—at the angle left scapula; and 9—at the left margin of the posterior spine. On the right side of the chest, positions 3R to 6R correspond to positions 3 to 6 on the left. Leads may also be taken from points one or two intercostal spaces higher or from one intercostal space lower. Position B is the same as 9, and E is the point on the epigastrium at the level of the ensiform cartilage.

THE PRESENT STUDY

A series of 200 complete thirty-lead electrocardiographic studies was analyzed in an effort to compare the findings over the precordium, using V, CR, CF, and CL leads. In all of the tracings, the 3 standard leads and the 3 unipolar limb leads were taken. In 46 tracings, only the V, CR, and CF leads were taken in positions 1 through 9. In 154 tracings the V, CR, CF, and CL leads were taken in positions 1 through 6, and in a few cases from positions 1 through 9. In all tracings, the chest electrode was held in the same position while the various leads were taken by means of turning the lead selector. In that manner, differences due to variation in position of the exploring electrode were avoided. Adults were used for all tracings.

The precordial leads were then analyzed and compared in an effort to demonstrate superiority in recording the precordial potentials. This included a demonstration of abnormalities present and the avoidance of registration of patterns which falsely suggested damage to the myocardium. The sets of tracings were compared after being grouped in the manner shown in Table I, which is a summary of the clinical material.

RESULTS

Normal Subjects.—The 82 subjects with normal hearts were divided into groups according to the electrical position. This is according to the criteria

proposed by Wilson and associates,[12] and depends upon comparison of the unipolar leads aV_L and aV_F with the precordial leads. In the vertical position, the ventricular complexes of Lead aV_L resemble those of V_1 and V_2, while the ventricular complexes of Lead aV_F resemble those of V_5 and V_6. In the semivertical position, the ventricular complexes of Lead aV_F resemble those of V_5 and V_6, but the QRS deflections of Lead aV_L are small. In the intermediate position, the ventricular complexes of Leads aV_L and aV_F are similar and like those of V_5 and V_6. In the semihorizontal position, the ventricular complexes of Lead aV_L resemble those of V_5 and V_6, while the QRS deflections of Lead aV_F are small. In the horizontal position, the ventricular complexes of Lead aV_L resemble those of V_5 and V_6, and the ventricular complexes of aV_F resemble those of V_1 and V_2. There is also an indeterminate position in which there is no obvious relationship between the QRS complexes of the limb leads and the precordial leads.

TABLE I. SUMMARY OF CLINICAL MATERIAL

Normal	82
Left bundle branch block (incomplete 3)	8
Right bundle branch block (incomplete 3)	7
Anteroseptal myocardial infarction	14
Anterolateral myocardial infarction	20
Posterior myocardial infarction	15
Posterolateral myocardial infarction	10
Anteroposterior infarction (right bundle branch block 2)	6
Subendocardial injury	9
Left ventricular hypertrophy	13
Right ventricular hypertrophy	4
Digitalis effects	6
Wolff-Parkinson-White syndrome	3
Chronic cor pulmonale	1
Rheumatic myocarditis	2
Total	200

A summary showing the incidence of inverted, low, or flat T waves is shown in Table II. In one subject, with vertical electrical position, the T in CF leads was negative from positions 1 through 6. In another (Fig. 1), also with no evidence of heart disease, the T waves were +/− in C_4F and negative in C_5F, and C_6F. In a third, also with vertical electrical position, the T waves were negative in C_1F, C_2F, C_3F, and C_6F, but they were upright in the V, CR, and CL leads. The CF leads in hearts with vertical electrical position had low R waves, particularly in positions 5 and 6, in 10 subjects. In the 3 electrocardiograms mentioned previously the CF leads would have been falsely interpreted as indicating an abnormality because of the negative T waves which were not due to myocardial changes, but were a result of strongly positive T waves in the left leg, which was serving as the indifferent electrode.

Of the 18 normal subjects with semivertical electrical position, the CF leads would have been considered suggestive of abnormality in 1 of the tracings

TABLE II. PRECORDIAL T WAVES IN NORMAL HEARTS

ELECTRICAL POSITION	NO. CASES	POSITION 1	POSITION 2	POSITION 3	POSITION 4	POSITION 5	POSITION 6
Vertical	15 (14 CL)	5 negative in V 1 −/+ in V 2 negative in CR 3 negative in CL 1 −/+ in CL 10 negative in CF	1 −/+ in V 1 −/+ in CL 5 negative in CF 1 +/− in CF	2 negative in CF	1 negative in CF 1 +/− in CF	2 negative in CF	3 negative in CF
Semivertical	18 (15 CL)	3 negative in V 1 +/− in V 4 negative in CL 1 +/− in CL 5 negative in CF 2 +/− in CF	1 negative in CF 1 +/− in CF		1 low + in CF	1 flat in CF 1 low + in CF	2 low + in CF
Intermediate	15	2 negative in V 1 flat in V 1 +/− in CR 3 negative in CL 3 negative in CF 1 +/− in CF	1 negative in CF			1 flat in CL	1 low + in CF
Semihorizontal	15	4 negative in V 1 −/+ in CR 4 negative in CL 1 +/− in CL 6 negative in CF				1 low + in CF	1 negative in CL 3 low + in CF
Horizontal	12	2 negative in V 2 negative in CR 2 negative in CL 2 negative in CF	1 negative in CF	1 +/− in CF		1 low + in CF	3 low + in CF
Indeterminate	7	2 negative in V 3 negative in CL 2 negative in CF 1 +/− in CF	1 negative in CF				1 low + in CF

because of a very low, upright T wave in positions 4, 5, and 6. Another tracing showed a flat T wave in C_5F and a low positive T in C_6F.

One normal subject with an intermediate electrical position and a high T wave in aV_L showed an isoelectric T wave in C_5L. In another subject in whom the heart was semihorizontal, the T waves were positive except for a diphasic minus-plus T in position 6 in the CL leads. Lead aV_L of this tracing showed a high R and T, and this high left arm potential of the T wave was held responsible for the diphasic T in position 6. In 3 other normal subjects with semihorizontal electrical position, T in C_6F was low but positive, and 1 of these also had a low but positive T in C_5F. In the 12 subjects with horizontal electrical position, the T waves were generally upright in position 1 (except for one patient), but 3 showed low positive T waves in C_6F and 1 also in C_5F.

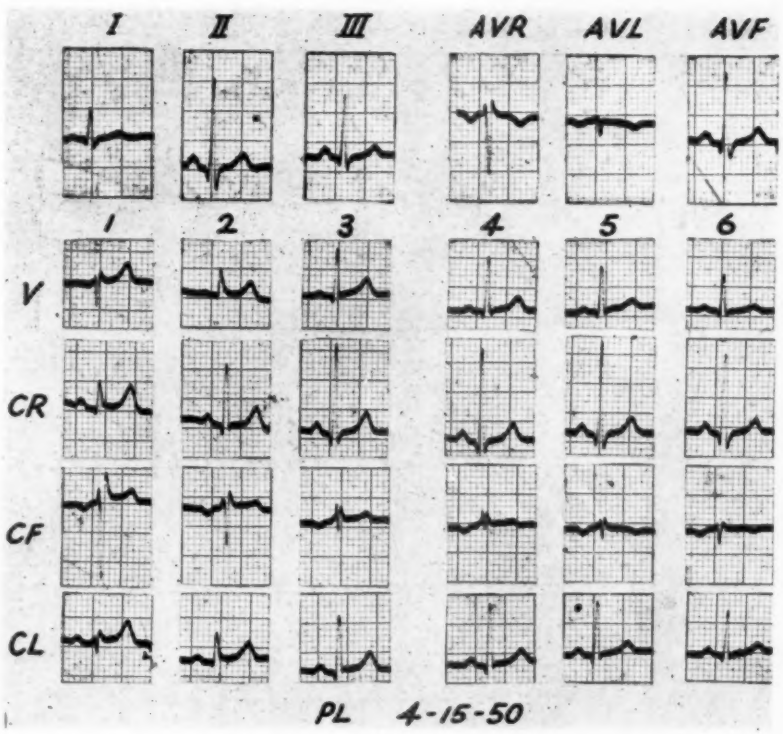

Fig. 1.—Comparison tracings of precordial leads of P. L., a 42-year-old asthenic white man, with normal vertical heart. CF leads show negative P waves, low QRS complexes, diphasic T wave in position 4, and negative T waves in positions 5 and 6.

In general, the R waves were lowest in the CF leads and highest in the CR leads, particularly in hearts with a vertical or semivertical electrical position. The P waves were more apt to be negative in the CF leads than in the others, and frequently in CF leads P waves were negative across the precordium from positions 1 to 6. T waves were frequently negative in position 1, most often in CF leads and in hearts in the vertical electrical position; negative T waves occurred less often in position 2.

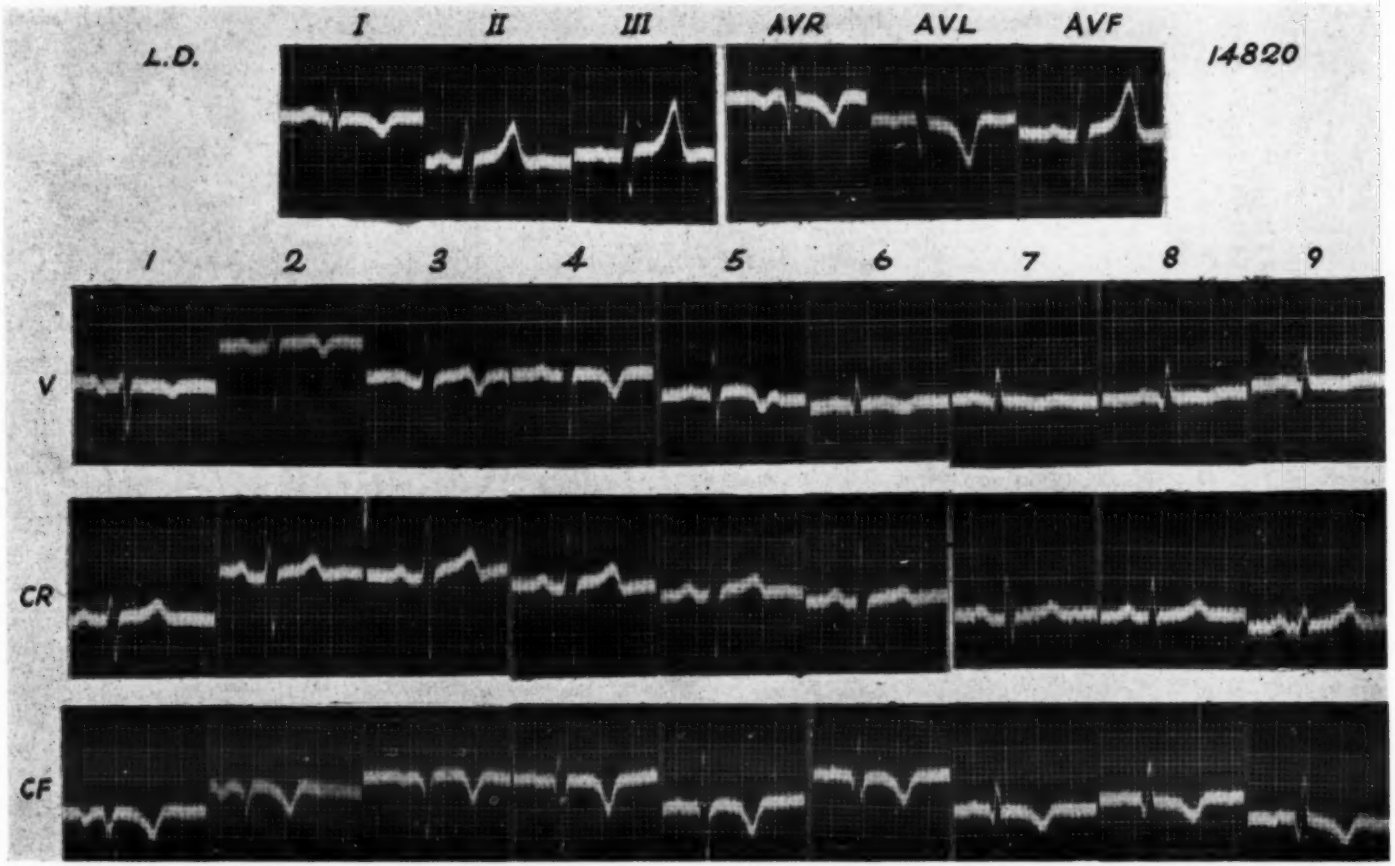

Fig. 2.—Comparison tracings of V, CR, and CF leads of L. D., a 45-year-old white woman with subacute high anterolateral myocardial infarction. Note the absence of T-wave changes in the anterior CR leads in contrast to the V and CF leads.

Bundle Branch Block.—Although the standard extremity leads can furnish the information for a presumptive diagnosis of bundle branch block, the block can be localized with certainty only by the precordial electrocardiogram. The late arrival of the impulse at the surface of the ventricle beneath the exploring electrode is represented by a late intrinsic deflection, usually with double-peaked R waves. This indicates a delay in impulse propagation to the area under the electrode. The late activation of the ventricle on the side of the block produces broad, slurred S waves over the uninvolved ventricle. If the QRS is 0.10 to 0.12 second in duration, the block is considered incomplete, while intervals over 0.12 second have been considered evidence of complete bundle branch block.

In 3 patients showing an incomplete left bundle branch block, 2 of whom had a semivertical electrical position of the heart, the characteristic pattern was observed best in V, CR, and CL leads and very poorly in CF. In 2 patients with complete left bundle branch block and intermediate electrical position, the diagnostic criteria were equally well shown in all leads. However, in 3 additional patients with complete left bundle branch block and horizontal electrical position, the CL leads failed to demonstrate the broad M-shaped QRS complexes with late intrinsic deflection shown in the other leads, even as far laterally as position 6. In 7 tracings showing right bundle branch block, which was incomplete in 3, there were no significant differences in the various types of precordial leads.

Anterior Myocardial Infarction.—Anteroseptal infarction denotes involvement of the anteroseptal portion of the left ventricle and is evidenced by signs of infarction in one or more of the first 4 precordial leads, but not in positions 5 and 6, or the standard limb leads, unless clockwise rotation on the longitudinal axis is present. Infarction of the anterior and lateral walls of the left ventricle produces changes also at positions 5 and 6 and is usually recorded in the limb leads.

The patients in this series were divided into groups showing 4 ancient and 10 recent anteroseptal infarctions, and 3 ancient and 17 recent anterolateral infarctions. In 7 of the patients with anteroseptal infarction and 10 with anterolateral infarction, the CL leads were not taken.

In 5 patients with recent anteroseptal infarction, the QRS and T-wave changes were more pronounced in the CF leads than in the others. In 3 of these 5, the changes extended to positions 5 and 6 in the CF leads, whereas they were not shown in these positions in the other leads. However, in another tracing, the transmural character of the lesion (evidenced by absent R waves) was not demonstrated in the CF leads but was well shown in the V and CR leads. In 1 case complicated by incomplete right bundle branch block, the Q waves were inconspicuous in the CR leads but prominent in the V leads, and it is possible that the lesion might have been missed if only the CR leads had been taken. In 2 patients with ancient anteroseptal infarction, 1 with intermediate and 1 with horizontal electrical position, the diagnostic signs were absent in CL, but they were present in CF leads and to a less pronounced degree in V and CR leads.

In 10 patients, the findings of anterolateral infarction were shown equally well in all leads. In one patient with high anterolateral infarction (Fig. 2), the ischemic T-wave pattern shown prominently in V and CF leads was com-

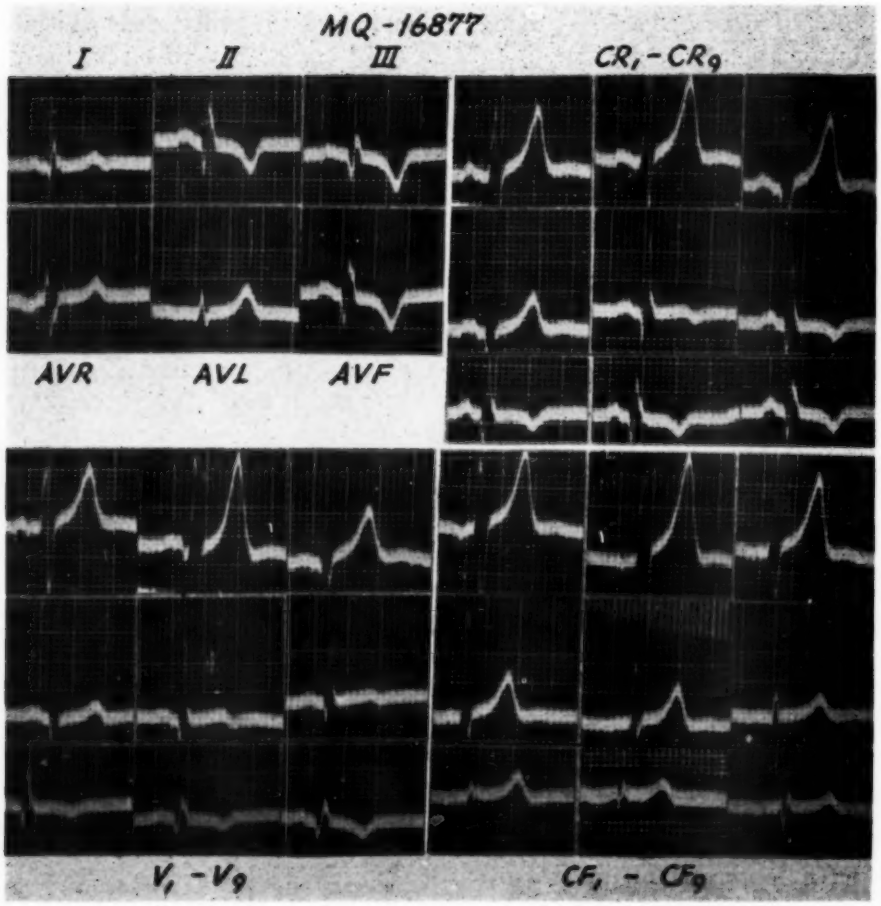

Fig. 3.—Comparison tracings of V, CR, and CF leads of M. Q., a 56-year-old white man with recent posterolateral infarction. Note the absence of diagnostic changes in the CF leads.

pletely missed by the CR leads. In another case, the V and CR leads demonstrated the transmural character of an infarct better than the CF leads. In 7 subjects, CF leads tended to show more pronounced, but probably false, changes in more positions on the chest wall than CR and V leads.

Posterior Myocardial Infarction.—Posterior myocardial infarctions are typically manifested by abnormal Q_2T_2 and Q_3T_3 patterns and by corroborative findings in aV_F. Lateral extension of such lesions may produce a small Q_1 and negative T_1, but it is usually evidenced by diagnostic patterns in precordial leads at positions 5 and 6. There usually are, in addition, reciprocal changes of posterior infarction in leads from the anterior precordium, consisting of early depression of ST segments and subsequent exaggeration of the R and T waves.

The tracings in this series were divided into 10 recent and 5 ancient posterior infarctions, and 8 recent and 2 ancient posterolateral infarctions. CL leads were

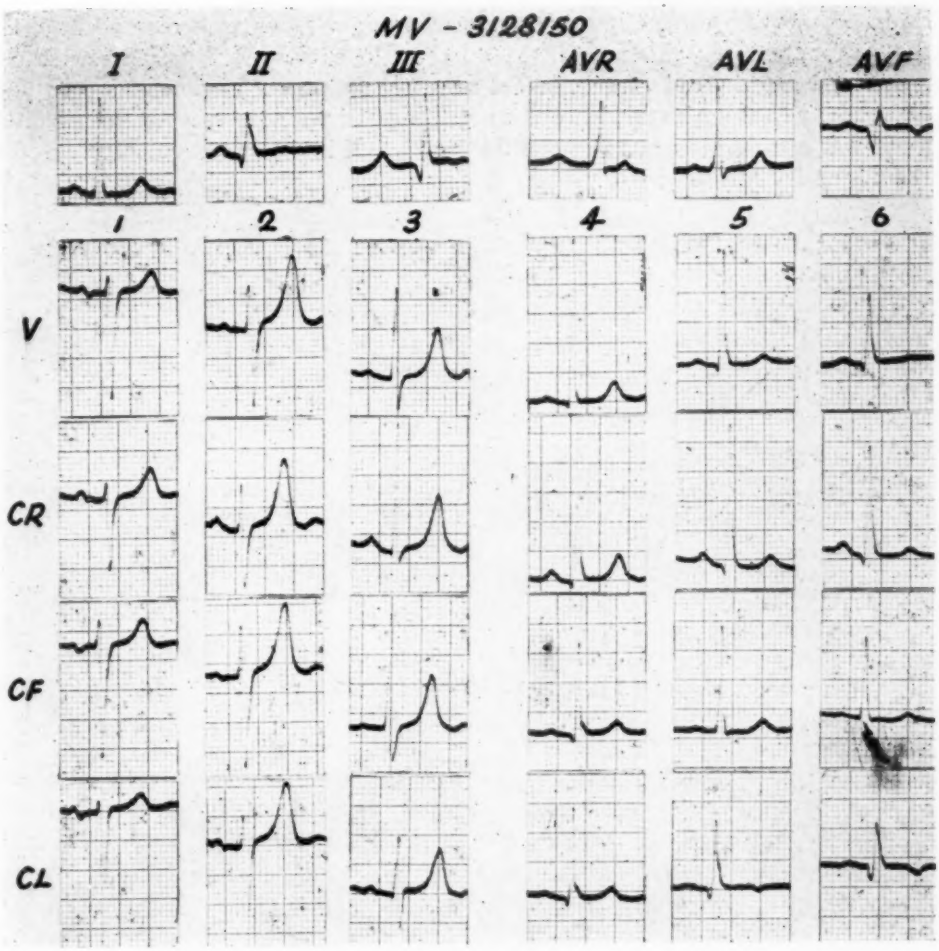

Fig. 4.—Tracings of V, CR, CL, and CF leads of M. V., a 67-year-old white woman with ancient posterolateral infarction. The lateral involvement is shown well in C_5L and C_6L, and to a less extent in V_6.

obtained in 16. In 5 patients with tracings showing posterior infarction, the infarction pattern was shown in positions 7 through 9 in V and CR leads, but not in CF. In another patient showing, in addition, signs of left ventricular hypertrophy, the CL leads were inferior to the other leads in showing the infarction pattern.

In 5 patients with recent posterolateral infarction, the diagnostic patterns were shown best in CL leads, but they were also shown well in CR and V leads. In none of these tracings was the lateral extension of the lesion demonstrated in the CF leads. The infarction pattern was completely missed by the CF leads even to position 9 in the tracings shown in Fig. 3. In 3 additional patients with recent posterolateral infarction, the lateral extension was poorly demonstrated in CF leads to position 6, and in 1 of these was also poorly shown in the CR

leads. However, the reciprocal changes of high T waves over the anterior precordium were best demonstrated by the CF leads. Of 3 patients with old posterior infarction, in 1 the changes were shown poorly in positions 6 to 9 in CF leads. In 2 patients with old posterolateral infarction, the lateral involvement was not demonstrated in the CF leads, and in 1 it was evidenced in only the CL and V leads (Fig. 4).

Anteroposterior Myocardial Infarction.—Although coexistent anterior and posterior infarction is not uncommon as a pathologic finding, it does not generally produce the classical infarction pattern in all 3 limb leads because of the tendency for the anterior and posterior effects to cancel out. It is usually evidenced by signs of the posterior infarction in Leads II, III, and aV_F with changes of infarction in the anterior precordial leads.

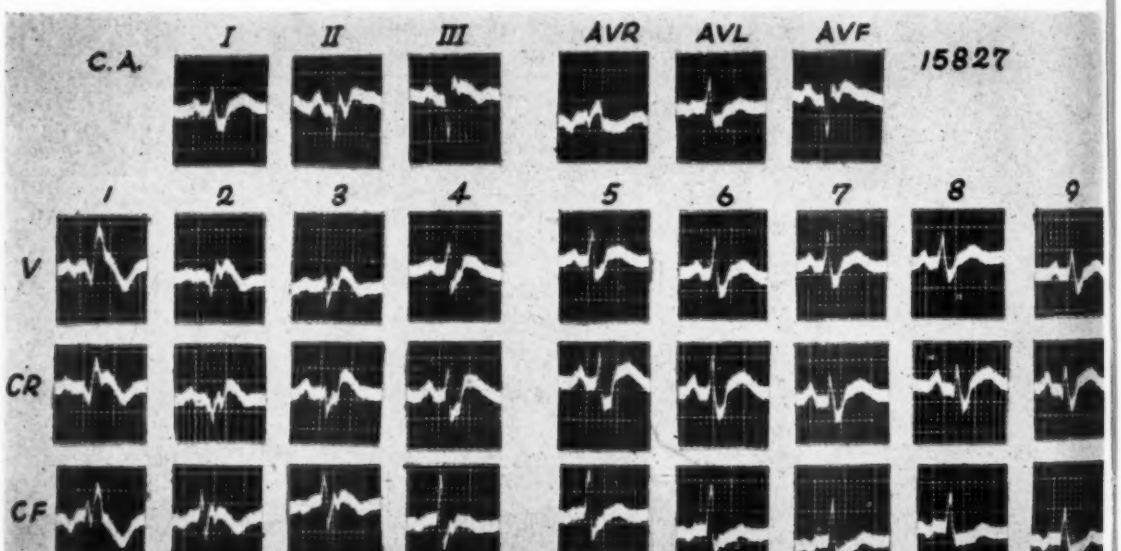

Fig. 5.—Comparison study of V, CR, and CF leads in C. A., a 51-year-old white man with anteroposterior infarction complicated by right bundle branch block. Anteroseptal involvement is demonstrated in the V and CR leads, but not in the CF leads.

Six patients showed evidence of anteroposterior infarction. In one, complicated by right bundle branch block, the anteroseptal involvement was not demonstrated in the CF leads (Fig. 5). In another, with right bundle branch block and two separate infarctions (Fig. 6), the diagnostic Q waves were not present in CF leads to position 9, but broad, slurred Q waves showed anterolateral and posterior involvement in V, CR, and CL leads. Tiny initial R waves were present in positions 2 and 3 of V and CL leads, but there were slurred Q waves in these positions in CR leads. In the other 4 patients, the various leads were considered equal in 3 in demonstrating the combination of anterior and posterior involvement, but CF leads were inferior, although still probably diagnostic, in 1.

Subendocardial Injury.—Ischemia of the myocardium is manifested in the electrocardiogram by T-wave changes and inversion, while ST deviations represent the current of injury. Subendocardial injury results in depression of the ST segments in the overlying precordial electrode and may be localized by its position on the chest wall. Q waves of abnormal form from the epicardial surface denote death of myocardial tissue, and thus are necessary in the diagnosis of myocardial infarction.

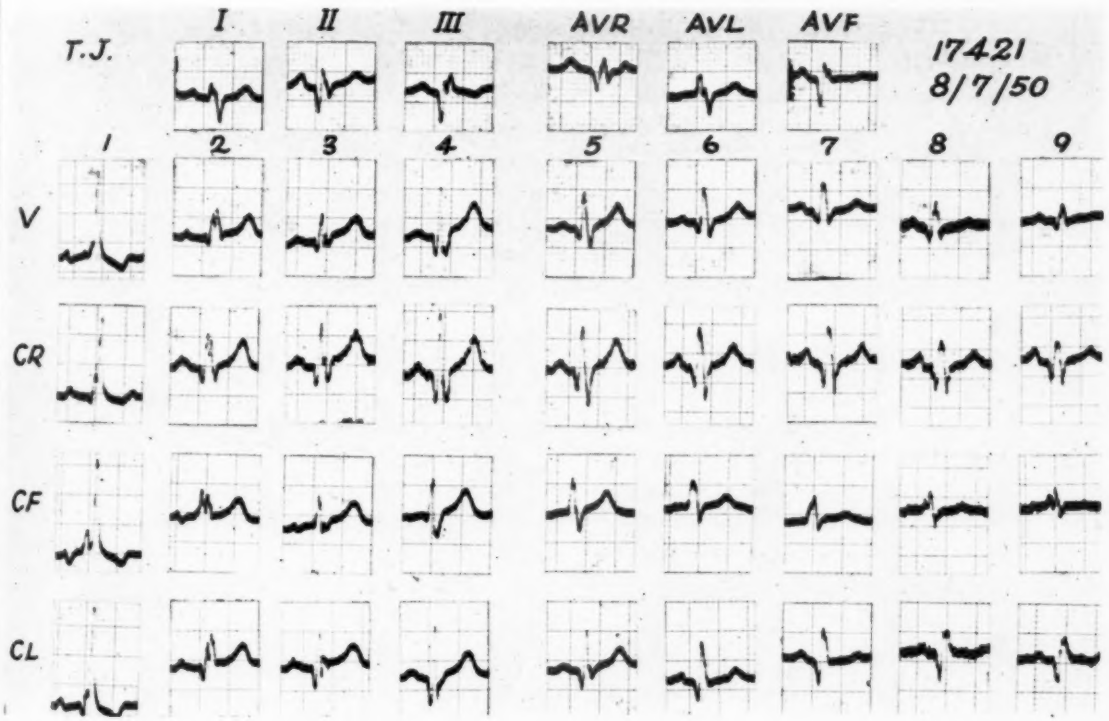

Fig. 6.—Complete set of V, CR, CL, and CF leads from positions 1 to 9 in T. J., a 62-year-old white man with two separate infarctions, anterolateral and posterior, complicated by right bundle branch block. The CF leads show a conspicuous absence of Q waves, which are demonstrated in the other combinations from positions 4 to 9. CR leads show, in addition, deep, slurred Q waves in positions 2 and 3.

Eight patients showed changes of subendocardial injury of the anterolateral wall of the left ventricle. In 4 patients, the electrical position of the heart varied from semivertical to semihorizontal. In 3 of these, the changes were shown equally in all leads. However, in 1 patient with a semivertical electrical position, V and CF leads showed the abnormality more definitely than CR and CL. In the 2 patients with horizontal electrical position, the changes were shown equally well by all leads in 1, but CF showed them most conspicuously in another. In 1 patient with posterolateral ischemia and intermediate electrical position, all leads showed the extension of the abnormality to the lateral wall.

Left Ventricular Hypertrophy.—In left ventricular hypertrophy leads from the right side of the precordium show small, early R waves and abnormally deep S deflections. Leads from the left side show abnormally tall, late R waves, usually preceded by Q waves, with late intrinsic deflection (over 0.045 second). The QRS complex tends to be slightly prolonged, usually measuring 0.09 to 0.11 second. There are frequently accompanying ST depressions and T-wave negativity in leads overlying the left ventricle, which have been ascribed as secondary to the QRS changes, but which we have considered as due to accompanying subendocardial injury and ischemia.

In the 13 patients in this group, the electrical position varied from horizontal to vertical. Seven patients also showed ST and T-wave changes in leads from the left ventricle. In 3 patients the CL leads were not taken. CL leads showed the characteristic configuration poorly in 3 patients in whom the position of the heart was horizontal, and both CR and CL showed the characteristics poorly in 1 patient in whom the position of the heart was semihorizontal. CF leads were inferior in showing the configuration in 1 patient with vertical electrical position. The V leads were characteristic in all patients.

Right Ventricular Hypertrophy.—Right ventricular hypertrophy shows a precordial pattern opposite to the normal, in which leads at positions 1 and 2 frequently have small Q waves and late, tall R waves (with delayed intrinsic deflection), while leads at positions 5 and 6 have early, small R waves and deep S waves. Four patients had tracings showing right ventricular hypertrophy with a chronic cor pulmonale pattern. The electrical position of the heart varied from vertical to semihorizontal. The V and CL leads tended to demonstrate the characteristic pattern better in the 2 patients in whom the heart had a vertical electrical position.

Miscellaneous.—In 6 patients with marked digitalis concave and depressed ST segments and diphasic minus-plus T waves, all chest leads showed the changes equally well. In 1 patient with a Wolff-Parkinson-White syndrome with vertical electrical position, the characteristics of the syndrome (i.e., the short P-R interval of 0.08 to 0.12 second and the broad, slurred upstroke of the R wave with prolonged QRS) were shown equally well in precordial leads V, CF, and CR over the left ventricle, but were shown poorly in CL. In 2 other patients with the Wolff-Parkinson-White syndrome, all the precordial leads were of equal value. In 1 patient with chronic cor pulmonale due to bronchiectasis, with semivertical electrical position, the CL lead in position 6 varied from the rest in showing a negative T. In 1 patient with rheumatic myocarditis and intermediate electrical position, V leads showed abnormality anteroseptally, CF leads showed abnormality anteriorly and posteriorly, and CR leads failed to show any abnormality at all. An anterior abnormality was presumed to exist by changes in the extremity leads, but interpretation would vary considerably, depending on the precordial leads used. In another patient with rheumatic myocarditis and limb leads showing evidence of posterolateral wall abnormality and vertical electrical position, CF leads as far laterally as position 6 did not show the T-wave negativity observed in V, CR, and CL leads.

Summary of Cases With Positive Findings in V Leads and Erroneous Findings in Others.—In this series, the CR leads failed to show the changes of rheumatic myocarditis in a patient with intermediate electrical position and failed to show the anterior ischemic pattern of high anterolateral myocardial infarction in another patient in whom the V and CF leads were effective. CR leads were inferior in demonstrating anteroseptal infarction in a patient with right bundle branch block and left ventricular hypertrophy in a patient with semihorizontal electrical position. The CF leads failed to show the anteroseptal involvement in 1 patient with right bundle branch block and anteroposterior infarction and the anterolateral and posterior involvement in another patient with right bundle branch block and anteroposterior infarction. C_7F to C_9F missed the posterior lesion in 5 patients with posterior myocardial infarction, and C_4F to C_6F missed the lateral extension of posterolateral infarction in 5 patients. The CL leads showed left ventricular hypertrophy poorly in 3 patients with horizontal electrical position and in an additional patient with semihorizontal electrical position. CL leads missed the diagnostic findings of anteroseptal infarction shown in other leads in 2 patients, 1 with intermediate and 1 with horizontal electrical position. The CF leads showed false abnormal patterns with T-wave inversions in positions 4, 5, and 6 in 3 patients with normal hearts. CL leads showed a false abnormal pattern with inversion of T in position 6 in one normal subject with semihorizontal position and in one patient with bronchiectasis.

DISCUSSION

The patterns displayed by the various precordial leads are a result of the potential differences between the exploring electrode and the extremity or terminal used as the indifferent electrode. As previous authors have observed, the results obtained from the leads using the right arm, left arm, or left leg as the attachment for the indifferent electrode can be estimated from the pattern obtained by the unipolar limb leads. Since the potential variations of the left arm and left leg are greatly affected by the electrical position of the heart, CL and CF leads show a great deal of variation.

In patients with a vertical electrical position, the high potentials of the left leg cause increased negativity in the CF leads. With a heart in a horizontal electrical position, the high potentials of the left arm cause increased negativity in the CL leads. While the positional variations in the CR leads are less, the low negative potentials of the right arm cause a uniform increased positivity in the CR leads. It is thus evident why negative P waves, low R waves, deep S waves, and low to occasionally negative T waves occur in CF leads in vertical hearts, and why the CF leads demonstrate so well the negative phases of anterior myocardial infarction. This, no doubt, is at least in part responsible for the former widespread adoption of IV F, which is now standardized by the American Heart Association Committee as C_4F, as the best precordial lead when only one precordial lead was being taken, as it would best demonstrate the changes of the very frequent uncomplicated anterior myocardial infarction.

On the other hand, the pattern of posterior infarction, and particularly any lateral extension, is shown poorly in CF leads and well in CL and CR leads because of the positive potentials at the left arm and right arm under such conditions, as contrasted to the prominent Q and negative T in the left leg.

While these observations were generally true in this series, some exceptions were noted as a result of complicating conditions such as conduction disturbances, accompanying abnormalities affecting the pattern of the unipolar limb leads, and variations in the electrical position of the heart.

It is significant that in this series none of the abnormalities were missed in the V or Wilson leads, and that we were not able to demonstrate false abnormalities in these leads.

CONCLUSIONS

1. In the majority of patients, there is no significant difference in the various precordial leads, V, CR, CF, and CL. Of these leads, CF and CL show the most variation from the other leads, depending on the electrical position of the heart.

2. False abnormalities may be obtained in CF and CL leads as a result of the electrical position of the heart. A normal heart with vertical or semivertical electrical position may produce negative T waves in CF leads, while a horizontal heart may produce flat to negative T waves in Leads C_5L or C_6L.

3. The pattern of uncomplicated anterior infarction is most markedly shown in the CF leads. However, CF leads may exaggerate the extent of the lesion.

4. The pattern of uncomplicated posterior and posterolateral infarction is most conspicuously shown in the V, CR, and CL leads. CF leads usually miss the changes, both posteriorly and laterally.

5. The V or Wilson leads can be depended upon to provide a reliable and true electrocardiographic diagnosis. For practical purposes, when only one set of precordial leads is obtained, the V or Wilson leads are superior. In contrast to the other lead connections, no significant abnormalities were missed, and no false abnormalities were obtained by the V leads in this series.

6. We would propose the designation W in honor of their originator, Dr. Frank N. Wilson, instead of V, which he and his associates applied to central terminal leads.

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THE aV LIMB LEADS IN THE DIAGNOSIS OF VENTRICULAR STRAIN

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THE recent widespread use of the augmented V (aV) limb leads in routine electrocardiography has demonstrated that they are of diagnostic value,[1] particularly in the diagnosis of ventricular strain.[2,3] It has long been realized that ventricular hypertrophy or strain may be associated in the electrocardiogram with an increased amplitude of the QRS deflections. Diagnostic value has been given to certain of these voltages,[2,3,4] permitting an accurate diagnosis of ventricular strain to be made in adults in the absence of abnormal S-T-T configuration. This has obvious clinical value and is of particular usefulness in the recognition of a pattern of early ventricular strain.

We have been impressed with the frequency with which apparently excessive voltages in the aV limb leads are observed in routine electrocardiograms. This has prompted us to examine the criteria of normality and of ventricular strain as particularly reflected by voltage change in the aV limb leads.

MATERIAL AND METHODS

Two hundred and thirty-seven electrocardiograms were examined in this study. Each record consisted of the standard and aV limb leads and the precordial leads V_1 to V_6. V chest leads were recorded with the central terminal[5] and the aV limb leads by the method of Goldberger,[6] modified by the introduction of a 5,000 ohm resistance into each connection of the indifferent electrode. The normal records and those showing left ventricular strain were obtained from adults; approximately one-half of the records showing right or combined ventricular strain were obtained from children. There were no instances of myocardial infarction, recent or remote, or of defective bundle branch conduction.

The electrocardiograms were selected from the files of the Heart Station on the basis of the contour in the standard limb leads and the V chest leads. The clinical history was then evaluated, and all cases in which this history was not compatible with the electrocardiographic interpretation (on the basis of the standard limb leads and V chest leads) were discarded, since we were interested in the aV lead findings in classical cases. The interpretation of a normal electrocardiogram was based on the criteria for normality in the standard limb

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leads[10] and V chest leads;[7,9] the diagnosis of left or right ventricular strain was based on known criteria for those interpretations in the standard limb leads and V chest leads;[2,3,4,9,10] the diagnosis of combined ventricular strain was based on criteria recently set forth from this department.[8] Thus, the records were selected without regard to the aV lead contours, the electrocardiographic diagnosis being based entirely on the standard limb and V chest leads. In each instance of an abnormal electrocardiogram the latter was compatible with the clinical diagnosis.

The amplitude of the various deflections of QRS in each of the aV limb leads was measured and analyzed in the manner described below. The amplitudes are reported in whole numbers except where the value was less than 1.0 mm. Amplitudes of 0.5 mm. or greater are recorded as the next largest whole number (e.g., 11.5 mm. equals 12.0 mm.); those less than 0.5 mm. are recorded as the immediately smaller whole number (e.g., 11.4 mm. equals 11.0 mm.). Since the "electrical" position is of obvious importance in this regard, the material in each group has been separated into one of the five positions as defined by Wilson.[9] In this paper, the use of the various positions from horizontal to vertical has reference only to the "electrical" position.

RESULTS

Normal Electrocardiograms.—There were 100 normal tracings, of which there were twenty in each of the five "electrical" positions. The data are presented in Table I. In general, the findings of Sokolow and Friedlander[7] have been con-

TABLE I. AMPLITUDES OF VARIOUS DEFLECTIONS IN THE aV LIMB LEADS IN 100 NORMAL ELECTROCARDIOGRAMS
(*Mean values and range of values are indicated.*)

ELECTRICAL POSITION	NO. CASES	AMPLITUDE OF VARIOUS DEFLECTIONS (MM.)					SUM OF aV_R AND aV_L OR aV_F‡ (MM.)	aV_R POSITIVE/ NEGATIVE§
		aV_R POSITIVE DEFLECTION*	aV_R NEGATIVE DEFLECTION	aV_L R WAVE	aV_F R WAVE	TOTAL VOLTAGE† (MM.)		
Vertical	20	1 (0–4)	8 (6–11)		11 (7–19)	26 (15–42)	19 (13–29)	0.2 (0–0.5)
Semivertical	20	1 (0–4)	8 (4–11)		8 (3–13)	23 (16–35)	15 (6–23)	0.1 (0–0.4)
Intermediate	20	1 (0–3)	10 (5–14)	5 (2–9)	6 (4–12)	26 (13–42)	18 (9–26)	0.1 (0–0.4)
Semihorizontal	20	1 (0–3)	8 (5–11)	8 (4–12)		24 (15–33)	16 (10–22)	0.1 (0–0.5)
Horizontal	20	1 (0–3)	6 (3–9)	7 (3–11)		25 (16–32)	13 (5–21)	0.3 (0–0.5)

*Refers to final upright deflection in aV_R.
†Refers to the sum of the amplitudes of all of the deflections of QRS in the three aV limb leads.
‡Sum of amplitude of negative deflection in aV_R and R wave in aV_L or aV_F.
§Ratio of final upright deflection to negative deflection in aV_R.

firmed. There was only one instance in which an R wave greater than 11.5 mm. was observed in aV_L. No instance of an R wave in aV_F greater than 19.0 mm. was encountered.

We found the maximum normal voltage of the final positive deflection in aV_R to be 4 mm. and the maximum normal amplitude of the negative deflection to be 14 mm. The three instances in which the negative deflection in aV_R exceeded 13 mm. occurred in intermediate hearts and in patients without demonstrable clinical cardiovascular abnormality. The amplitude of the final R wave never equalled or exceeded that of the negative deflection in aV_R.

The total voltage of the aV limb leads, obtained by summating the amplitudes of all of the QRS deflections in all three leads in the usual manner, varied from 13 mm. to 42 mm. The sum of the amplitudes of the inverted deflection in aV_R and the R wave in aV_L or aV_F varied from 5 to 29 mm., depending upon the "electrical" position (Table I). The value for the ratio of the final positive deflection to the negative deflection in aV_R ranged from zero to 0.5, never exceeding the value of 0.5; if the value was other than zero, it usually lay between 0.3 and 0.5.

Left Ventricular Strain.—There were 100 electrocardiograms in this group, divided equally among the five "electrical" positions. There were forty-one records in which no characteristic S-T-T deviations were present in the aV limb leads. The remaining fifty-nine records displayed S-T-T abnormalities ranging

TABLE II. AMPLITUDES OF VARIOUS DEFLECTIONS IN THE aV LIMB LEADS IN 100 ELECTROCARDIOGRAMS EXHIBITING LEFT VENTRICULAR STRAIN PATTERNS

(Mean values and range of values are indicated.)

ELECTRICAL POSITION	NO. CASES	AMPLITUDE OF VARIOUS DEFLECTIONS (MM.)					SUM OF aV_R AND aV_L OR aV_F‡ (MM.)	aV_R POSITIVE/ NEGATIVE§
		aV_R POSITIVE DEFLECTION*	aV_R NEGATIVE DEFLECTION	aV_L R WAVE	aV_F R WAVE	TOTAL VOLTAGES† (MM.)		
Vertical	20	1 (0–3)	11 (3–18)		15 (9–21)	37 (25–62)	25 (16–38)	0.08 (0–0.3)
Semivertical	20	1 (0–4)	12 (7–22)		12 (6–17)	35 (19–69)	24 (14–39)	0.09 (0–0.4)
Intermediate	20	1 (0–3)	13 (6–28)	9 (3–16)	12 (4–27)	34 (16–70)	23 (9–54)	0.04 (0–0.2)
Semihorizontal	20	0.5 (0–2)	11 (4–18)	12 (4–18)		35 (13–62)	23 (14–36)	0.03 (0–0.2)
Horizontal	20	0.5 (0–2)	10 (3–18)	14 (5–18)		38 (21–54)	25 (12–31)	0.1 (0–0.3)

*Refers to final upright deflection in aV_R.
†Refers to the sum of the amplitudes of all of the deflections of QRS in the three aV limb leads.
‡Sum of amplitude of negative deflection in aV_R and R wave in aV_L or aV_F.
§Ratio of final upright deflection to negative deflection in aV_R.

from slight depression of the S-T segment to the classical S-T-T pattern of left ventricular strain.[10]

The data are presented in Table II. Certain differences from the normal group deserve emphasis. The negative deflection in aV_R tended to be deep, exceeding 14 mm. in about 25 per cent of the cases (Fig. 1,*A*). Since the amplitude of the R wave in aV_F rarely exceeded the maximum normal value of 19 mm. (Fig. 1,*A*), it did not prove of great value as a single criterion of left ventricular strain in this study.

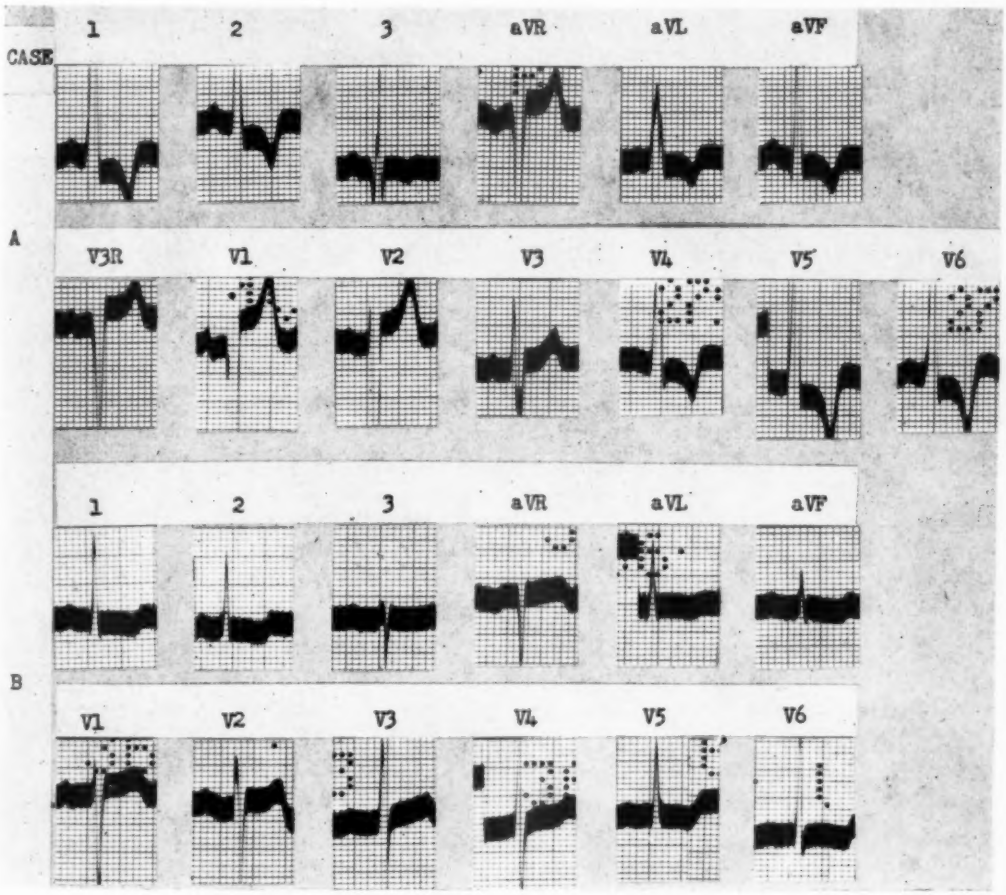

Fig. 1.—*A*, Definite pattern of left ventricular strain. Intermediate "electrical" position of the heart. Record obtained from a 45-year-old woman with rheumatic, aortic, and mitral valvular lesions. *B*, Left ventricular strain in an intermediate "electrical" position of the heart. Lead aV_R demonstrates the S-T-T contour of strain; Leads aV_F and aV_L are not diagnostic, though compatible. Record obtained from a 50-year-old man with hypertensive heart disease.

The amplitude of the R wave in aV_L proved of distinct value, exceeding the normal maximum voltage of 12 mm. in twenty-nine of forty semihorizontal and horizontal hearts (Fig. 1,*A*). The total voltage of all QRS deflections in the

three aV leads exceeded the normal maximum value in each respective electrical position in about 50 per cent of the cases (Fig. 1,*A*). The sum of the negative deflection in aV_R and the positive deflection in aV_L or aV_F also exceeded the maximum normal value in each "electrical" position in about 50 per cent of the cases (Fig. 1,*A*). The final positive deflection in aV_R was never equal to nor did it exceed the amplitude of the negative deflection. The value for the ratio of the former to the latter deflection ranged from zero to 0.4, exceeding 0.3 in only three of the 100 cases.

Excessively large voltages were observed in instances with and without abnormal S-T-T configurations. The abnormal S-T-T contour indicative of left ventricular strain in aV_L or aV_F consists of an S-T segment which is depressed and coved upward and an inverted, asymmetrical T wave, depending upon which lead resembles the left chest leads; the reciprocal pattern of an S-T segment which is elevated and coved downward and an upright T wave occurs in aV_R, closely resembling the pattern of the right chest leads. In several instances, the S-T-T pattern in aV_L or aV_F, while compatible, was not diagnostic of strain, but displayed the contour of left ventricular strain in aV_R (Fig. 1,*B*).

Right Ventricular Strain.—The twenty-seven instances of right ventricular strain patterns in this study exhibited only vertical or horizontal positions; the data obtained from these records are presented in Table III. The total voltage of all QRS deflections in the three aV leads in the majority of cases exceeded those of the normal group and occasionally were larger than the similar values in the left ventricular strain group. However, this may in part be due to the

TABLE III. AMPLITUDES OF VARIOUS DEFLECTIONS IN THE aV LIMB LEADS IN 27 ELECTROCARDIOGRAMS EXHIBITING RIGHT VENTRICULAR STRAIN PATTERNS

(Mean values and range of values are indicated.)

ELECTRICAL POSITION	AGE GROUPING	NO. CASES	AMPLITUDE OF VARIOUS DEFLECTIONS (MM.)					aV_R POSITIVE/ NEGATIVE§
			aV_R POSITIVE DEFLECTION*	aV_R NEGATIVE DEFLECTION	aV_L R WAVE	aV_F R WAVE	TOTAL VOLTAGES†	
Vertical	18 months to 15 years	9	6 (3–12)	8 (2–11)	4 (3–7)	9 (5–20)	38 (26–65)	0.9 (0.3–2.5)
	Over 15 years	11	6 (1–15)	6 (0.5–15)	4 (0–17)	9 (0–19)	37 (9–64)	1.7 (0.2–6)
Horizontal	2 years to 4 years	3	6 (5–7)	5 (3–8)	4 (2–6)	8 (1–15)	33 (23–49)	1.2 (0.7–1.6)
	Over 15 years	4	7 (5–11)	3 (0–7)	2 (1–3)	8 (1–15)	35 (18–53)	2.8 (1–5)

*Refers to final upright deflection in aV_R.
†Refers to the sum of the amplitudes of all of the deflections of QRS in the three aV limb leads.
§Ratio of final upright deflection to negative deflection in aV_R.

fact that about 50 per cent of the records in this group were obtained from children with rheumatic or congenital heart disease.

Burchell has recently emphasized the frequency with which a tall late R or R′ occurs in Lead aV_R in infants.[11] The experience of this department[12,13] as well as that of others[14] demonstrates that an adult form of aV limb lead electrocardiograms may be expected after 18 months of age. We have therefore not included patients younger than 18 months of age in this study. However, the distinction has been made between tracings obtained from children (18 months to 14 years) and adults (15 years of age and older).

The final positive deflection in aV_R tended to be larger in all age groups than in the other groups and exceeded the maximum normal adult value of 4 mm. in seven of the fifteen adult cases (Fig. 2,*A* and *B*). Moreover, it exceeded the maximum normal value of 4.5 mm. in children over 1 year of age in nine of the twelve cases in the younger age group.[12,13]

The amplitudes of the R and S waves in Leads aV_L and aV_F have been determined and the R/S ratio calculated in each instance. Table IV presents the results obtained by summating the values for the R/S ratio in aV_L and that in aV_F. There was a definite tendency for these values to differ in the three groups of cases; thus, the value was often smaller than the minimum normal values in cases of right ventricular strain (Fig. 2,*A*) and larger than the maximum normal value in cases of left ventricular strain. The sum of the R/S ratio in the aV limb leads may therefore be of diagnostic value.

TABLE IV. RATIO OF AMPLITUDE OF R TO S WAVES; THE SUM OF THE VALUE FOR THE R/S WAVE RATIOS IN LEADS aV_L AND aV_F
(*Mean values and range of values are indicated.*)

ELECTRICAL POSITION	NORMAL PATTERN	LEFT VENTRICULAR STRAIN PATTERN (OVER 15 YEARS OF AGE)	RIGHT VENTRICULAR STRAIN PATTERN	
			OVER 15 YEARS OF AGE	BETWEEN 1½ AND 15 YEARS OF AGE
Vertical	11.4 (4.4–20)	13.4 (2.5–21.5)	6.2 (0.5–14)	4.6 (2.2–7.0)
Horizontal	9.2 (6.3–13.5)	17.2 (6.3–70.3)	2.6 (0.6–7.0)	6.6 (2–15)

Whenever the final positive deflection in aV_R equalled or exceeded the amplitude of the inverted deflection, a pattern of right ventricular strain was observed in the precordial leads (Fig. 2,*A* and *B*). The ratio of the final positive to the inverted deflection in aV_R was never less than the value 0.2 in instances of right ventricular strain. A value exceeding 0.6 for this ratio was encountered only in instances of right ventricular strain.

S-T-T configuration in the aV limb leads did not contribute to the diagnosis of right ventricular strain, a sharp contrast to the state of affairs in left ventricular strain.

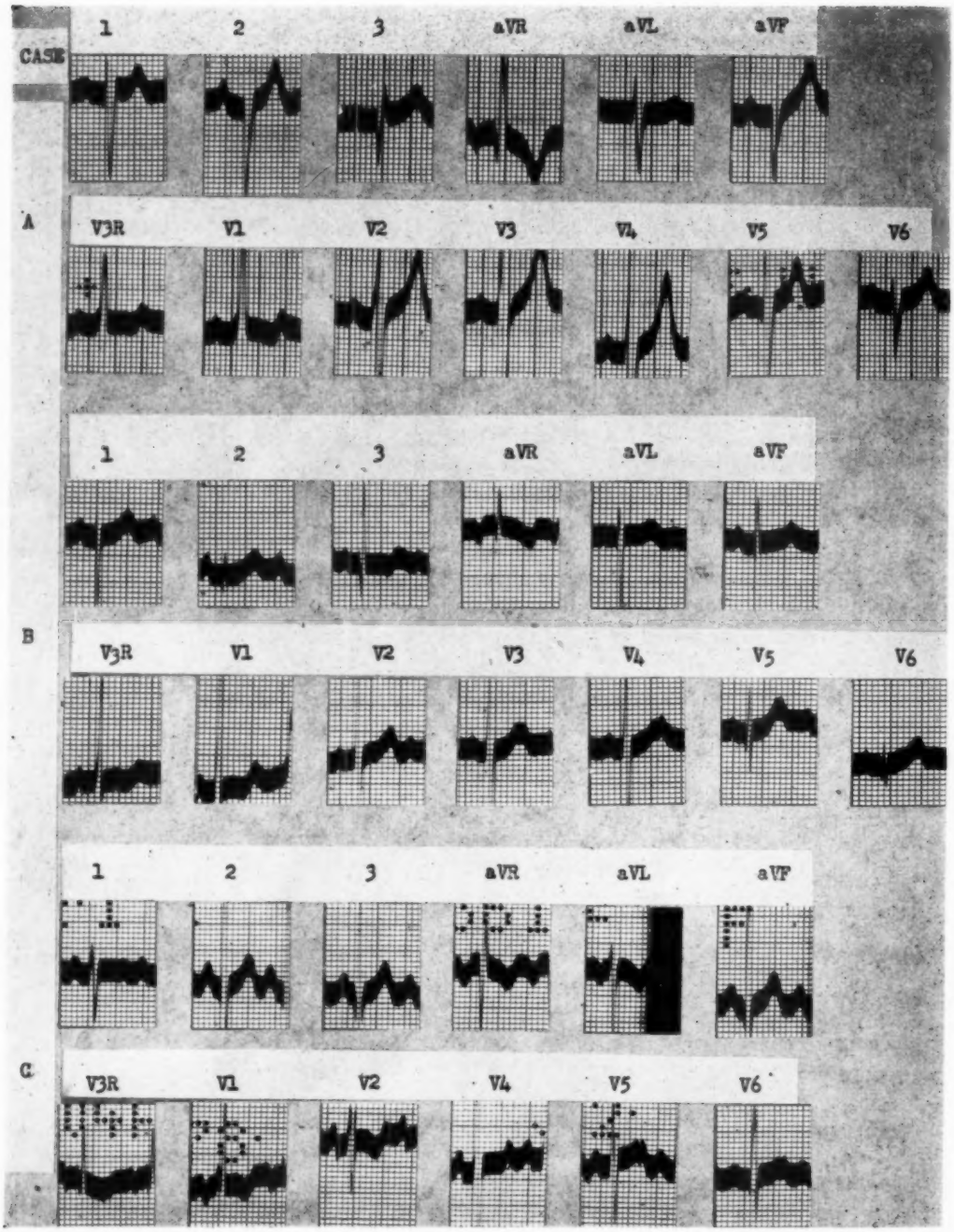

Fig. 2.—*A*, Definite pattern of right ventricular strain. The pattern in Lead aV_R is diagnostic. Record obtained from a 16½-year-old boy with congenital heart disease. *B*, Right ventricular strain. Lead aV_R is diagnostic. Record obtained from a 66-year-old woman with hypertensive and arteriosclerotic heart disease. *C*, Definitive pattern of right ventricular strain in the precordial leads. The aV leads demonstrate abnormally large voltages in the absence of a pattern consistent with left ventricular strain. Record obtained from a 3-year-old male child with congenital heart disease.

Combined Ventricular Strain.—During a recent study of this problem in this laboratory[8] evidence of concomitant left and right ventricular strain was observed in ten electrocardiograms. These tracings were examined, and it was noted that the aV lead voltages often were strikingly smaller than those of the precordial leads. However, the paucity of such cases prevented conclusive statistical data in this regard.

DISCUSSION

In the absence of diagnostic S-T-T changes the electrocardiographic interpretation of left or right ventricular strain may be difficult. Certain characteristically large voltages in the aV limb leads,[2,3] as in the standard limb[4] and precordial leads,[9] have been found of value in this regard. Various explanations have been given for the occurrence of increased voltages of QRS deflections and the characteristically altered S-T-T configurations in the presence of ventricular strain and/or hypertrophy.[4,9,10] These will not be discussed here.

Valuable diagnostic criteria of left ventricular strain were found in this analysis. While they should not alone be considered as diagnostic, they may serve to draw attention to the probability of the existence of left ventricular strain. They include an R wave in aV_L exceeding 12 mm. in amplitude in adults, a total aV limb lead voltage (sum of amplitude of all the deflections of QRS in the three aV leads) definitely in excess of that normally found in each respective "electrical" position, and an abnormal sum of the amplitudes of the negative deflection in aV_R plus that of the R wave in aV_L or aV_F, depending upon the "electrical" position (Tables I and II). An R wave exceeding 19 mm. in aV_F in an adult was suggestive of left ventricular strain but was observed infrequently.

There were twenty-five records in which a definitive S-T-T pattern of left ventricular strain was not seen in either the standard limb leads or the precordial leads. These records demonstrated either no changes in S-T-T or, at most, a minimal T-wave flattening and S-T deviation. In fourteen of these the voltages in the V chest leads were greater than normal.[7] In twelve instances the total QRS voltages of the aV limb leads exceeded normal. In fifteen instances there was an abnormal sum of the amplitudes of the negative deflection in aV_R and the R wave in aV_L or aV_F. There were four instances in which excessive voltages were encountered only in the V chest leads. There were two instances in which abnormal voltages were encountered only in the standard and aV limb leads. There were two other instances in which abnormally large voltages were encountered only in the aV limb leads.

The value of Lead aV_R in the interpretation of left ventricular strain has not been previously emphasized. Both S-T-T contour and QRS amplitude were found to be of value, the characteristic abnormal S-T-T being a definitive adjunct in this diagnosis. Further, the deep negative deflection of QRS in such cases proved of considerable help, both as a single diagnostic criterion of strain and in the sum obtained by adding its amplitude to that of aV_L or aV_F in the different positions.

In the diagnosis of right ventricular strain (hypertrophy) as regards voltage changes in the aV leads, an R wave in aV_R exceeding 4 mm. in adult records proved of diagnostic help. An R wave in aV_R exceeding 5 mm. occurred in

fifteen of the twenty-seven cases and may be diagnostic of right ventricular strain in patients over 2 years of age if right bundle branch block can be excluded. In the absence of a definitively abnormal or borderline tall R wave in aV_R, the diagnosis of right ventricular strain is difficult to make merely from the aV lead contour; in this regard, in the absence of an aV limb lead contour compatible with the diagnosis of left ventricular strain, the presence of an abnormally large total aV lead voltage is suggestive of right ventricular strain (Fig. 2,*C*). Thus, the total aV limb lead voltage is of value in the interpretation of right ventricular strain.

The sum of the R/S amplitude ratio in Leads aV_L and aV_F (Table IV) showed definite variations in the three groups of records studied but often failed to present diagnostic criteria. Various QRS and T-wave ratios other than those recorded here or previously[2,3] were calculated but failed to prove of any value. Lead aV_R proved of great value other than as already described. When the final positive deflection in aV_R in adult tracings was equal in amplitude or exceeded that of the negative deflection, it was found to present a diagnostic criterion of right heart strain. When the value for the ratio of the amplitude of the final upright deflection in aV_R to that of the inverted deflection exceeded 0.7, it was definitely suggestive of right ventricular strain in adults.

The criteria we have presented are to be applied only in the absence of defective intraventricular conduction and/or myocardial infarction. These criteria will be subjected to further tests in an unselected run of successive records routinely obtained in the Heart Station.

SUMMARY

The amplitude of each deflection in Leads aV_R, aV_L, and aV_F has been measured in 100 normal electrocardiograms and in 137 tracings indicative of left, right, or combined ventricular strain, as judged by the standard limb and precordial leads. In each instance, the data obtained have been separated into respective groups, depending on the "electrical" position with reference to the anteroposterior axis of the heart.

Criteria indicative of left ventricular strain in adults were found to include an R wave in a V_L exceeding 12 mm. in amplitude, an R wave in aV_F exceeding 19 mm., and a value for the sum of the inverted deflection in aV_R and the positive deflection in aV_L or aV_F exceeding the maximum found normally in the respective "electrical" position.

Criteria indicative of right ventricular strain included a final positive deflection in aV_R greater than 4 mm. in amplitude in adults and greater than 5 mm. in children over 2 years of age. When the value for the sum total of all deflections of the QRS in the three aV limb leads exceeded that found normally and when the aV limb lead pattern was not compatible with left ventricular strain, the precordial leads demonstrated right ventricular strain.

The contour and voltage changes of the different deflections in Lead aV_R have been found of distinct value in the diagnosis of ventricular strain. In adults a negative deflection in aV_R greater than 14 mm. is suggestive of left

ventricular strain; when the final upright deflection exceeds 4 mm., it is suggestive of right ventricular strain; when the final upright deflection equals or exceeds in amplitude the negative deflection or when the ratio of the former to the latter exceeds 0.7, it is indicative of right ventricular strain.

We are indebted to Dr. A. Pick for his valuable suggestions.

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WATER AND ELECTROLYTE BALANCE DURING RECOVERY FROM SEVERE CONGESTIVE FAILURE ON A 50 MILLIGRAM SODIUM DIET

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THE importance of diet in the treatment of congestive failure has been long recognized. The time-honored Karell regimen, consisting merely of 800 ml. of whole milk daily, enabled many patients to regain compensation, but it failed in the more severe cases because of insufficient limitation of sodium intake (400 mg.), yet too drastic a restriction in other essential ingredients. Greater success has been obtained with modern cardiac diets, supplying 200 to 400 mg. of sodium daily, but refractory cases of severe congestive failure are still encountered. The purpose of this study was to determine the clinical efficacy of a 50 mg. sodium diet in severe cardiac failure and to investigate balances of water, sodium, potassium, chloride, and nitrogen during recovery.

DIET

The diet consisted of 2,000 ml. of Lonalac formula and 500 ml. of orange juice with 30 Gm. of added sugar. The Lonalac formula was prepared as follows: Lonalac powder 250 Gm., sugar 125 Gm., and water 2,000 ml. The formula was flavored with vanilla and was kept chilled. Four hundred ml. of this were given five times a day. Table I shows the composition of the 50 mg. sodium diet.

TABLE I. COMPOSITION OF THE 50 MG. SODIUM DIET

Water	2,500 c.c.
Sodium	2.25 meq. (50 mg.)
Potassium	108.30 meq. (4,330 mg.)
Chloride	36.97 meq. (1,320 mg.)
Protein	67.50 Gm.
Carbohydrate	320.00 Gm.
Fat	70.00 Gm.
Calories	2,150

This diet furnished sufficient calories, protein, and water and was made adequate in vitamins by the use of crystalline supplements. It was liberal in respect to potassium, but extremely low in sodium content.

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MATERIAL

The foregoing diet was given to nine patients with severe congestive failure. One patient was forced to discontinue the diet after the fourth day because of diarrhea and was excluded from this report because of incomplete collection of excreta, consequent upon urinary and fecal incontinence. Another patient refused the diet after the first day, due to nausea and vomiting, and was therefore excluded from the metabolic study. The other seven patients tolerated the diet well for the period of study, which ranged between eight and sixteen days. Clinical and metabolic balance data on these seven patients form the basis of this report.

Prior to the institution of the 50 mg. sodium diet, four of the patients had proved refractory to a standard low-sodium diet, digitalization, and mercurial diuretics given in the hospital for periods of nine, ten, fourteen, and forty-nine days, respectively; two others became progressively decompensated on a similar regimen carried out in the home; and the remaining patient showed increasing anasarca, despite full digitalization at home. At the advent of the metabolic study, there were marked passive congestion and edema of both the systemic and pulmonary circuits in four of the patients, and marked passive congestion of the lungs, but little or no clinically detectable peripheral edema, in the other three patients.

The clinical diagnoses were as follows: rheumatic mitral stenosis and insufficiency and aortic insufficiency in two patients (L. C. and M. W.); rheumatic mitral stenosis and insufficiency in two patients (M. F. and K. B., the latter complicated by hypertension); hypertensive heart disease in two patients (K. W. and J. D.); and arteriosclerotic heart disease associated with the Kimmelstiel-Wilson syndrome in one patient (J. T.).

METHOD

The degree of cardiac compensation was evaluated from clinical examination, six-foot roentgenogram, venous pressure, arm-to-tongue circulation time, vital capacity, plasma volume, using T 1824,[1] and body weight, determined on a Troemer beam balance, sensitive to 10 Gm. at full load. Electrocardiograms, employing multiple precordial leads and standard and augmented unipolar limb leads, were taken during the control period in all patients and were repeated at the end of the metabolic study in five patients.

During the metabolic studies, the patients were segregated in small rooms under the constant supervision of a special nurse trained to keep accurate records of intake and to make full collections of excreta. Balance studies for water, sodium, potassium, chloride, and nitrogen were carried out in the seven patients for total periods of eight to sixteen days. Frequent determinations of plasma concentrations of the foregoing elements were made before, during, and after the balance study. Insensible loss of water was determined in five of the patients by the method of Newburgh.[2] None of the patients showed visible evidence of perspiration, and no efforts at collection of sweat were made. Stools were analyzed in three. None of the seven patients exhibited diarrhea or vomiting during the course of the balance study.

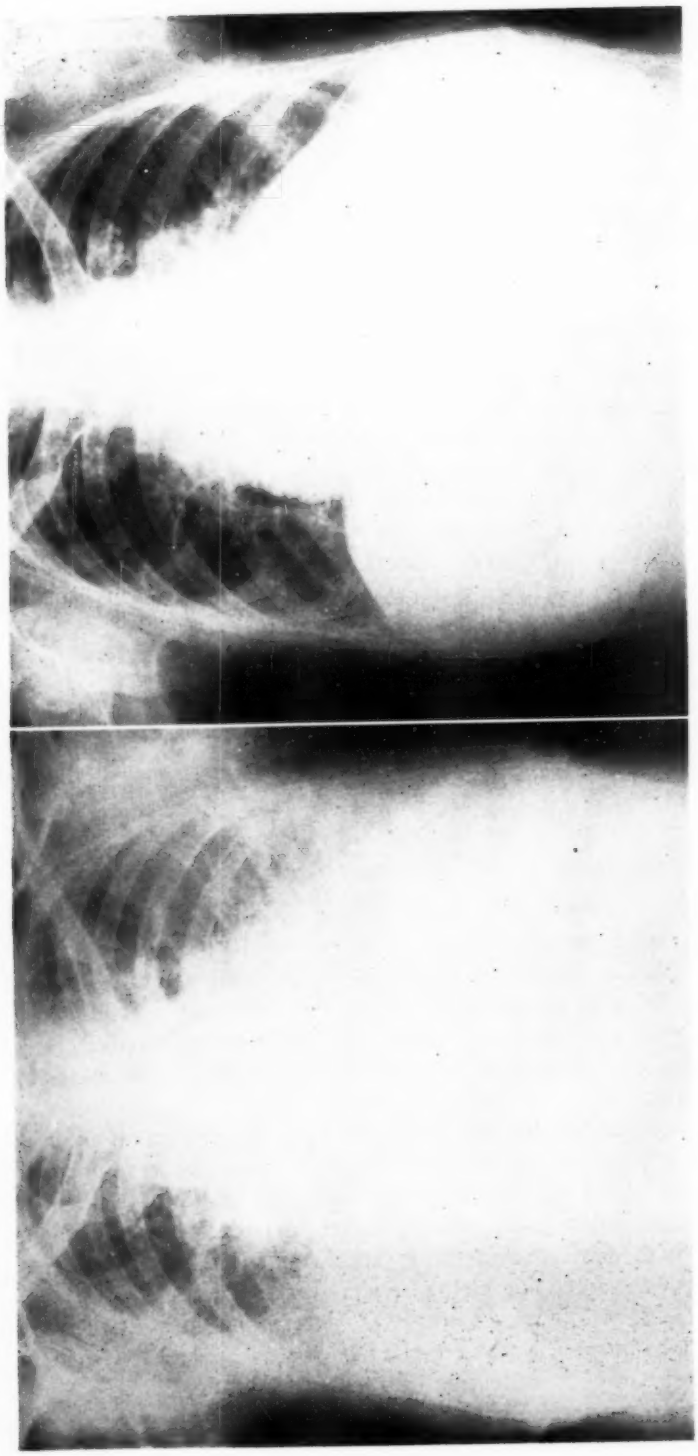


Fig. 1.

Intracellular and extracellular partitions were calculated according to the method of Darrow.[3] Reference point for the total extracellular volume of water was selected at the end of the study when edema had been eliminated, 20 per cent of the body weight being taken as equivalent to the extracellular water at that moment. Calculations of extracellular water were then carried back to the initial period, utilizing the total chloride balances and plasma chloride concentrations. In one patient (K. B.), who was still slightly edematous at the end of the study, 30 per cent of the edematous weight at the onset of the study was taken as the reference point of extracellular water. Primary interest was not in the absolute volume of extracellular water, but rather in the changes of extracellular water (and consequently changes in extracellular electrolytes).

Sodium and potassium were analyzed according to methods described by Mosher and associates.[4] Chloride was determined manometrically.[5] Nitrogen was determined by micro-Kjeldahl method.[6] Studies were divided into periods of three to five days.

CASE REPORTS

CASE 1.—J. T., a 64-year-old white woman, was admitted to Receiving Hospital on Dec. 25, 1949, with massive anasarca due to congestive failure. Diabetes mellitus and hypertension were known to have been present for three years. Cardiac decompensation became manifested about two years prior to admission and became refractory to treatment during the last two months.

Physical Examination.—On admission marked orthopnea and cyanosis were revealed. The blood pressure was 170 mm. Hg systolic and 100 mm. Hg diastolic. There was bilateral retinitis proliferans. Jugular veins were distended. Physical and roentgen examination of the chest revealed marked pulmonary congestion and a bilateral pleural effusion. The left cardiac border extended 11 cm. from the midline and the right border, 6 cm.; the cardiothoracic ratio was 65 per cent. There was a protodiastolic gallop rhythm at the apex. A tender liver occupied the entire right upper quadrant and the medial half of the left upper quadrant. Moderate ascites was found. Massive edema was present over the arms, legs, and back.

Laboratory Studies.—The urine showed 4 plus albumin and 30 white blood cells per high-power field. Blood hemoglobin was 13 Gm. per cent, blood urea nitrogen 32 mg. per cent, and total serum proteins 6.16 Gm. per cent. Fasting blood sugars ranged from 112 mg. per cent to 172 mg. per cent throughout hospitalization, and urine was consistently sugar free. Serial electrocardiograms showed evidence of an old anterolateral myocardial infarct.

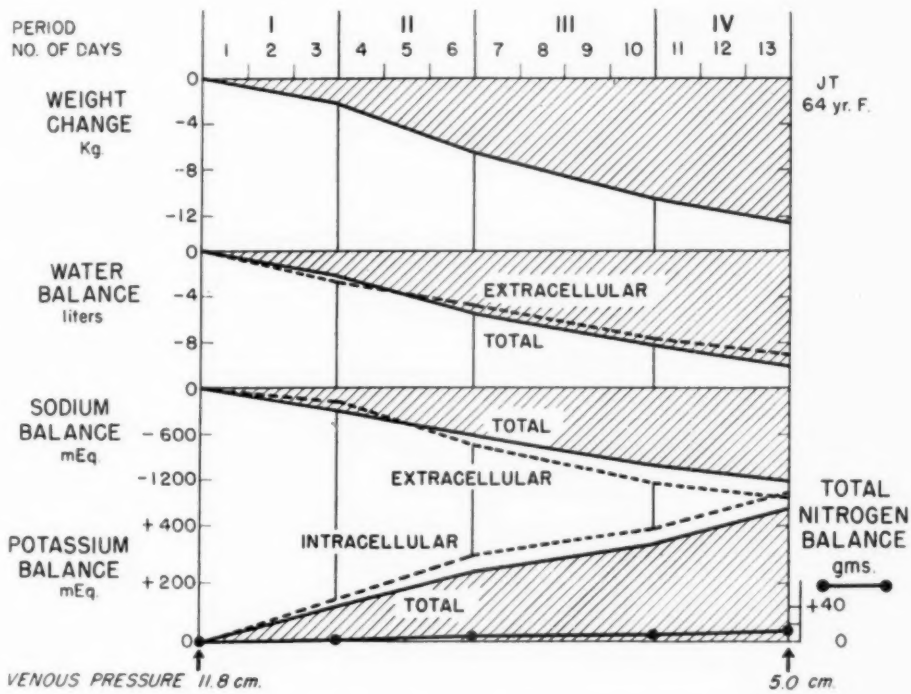
Course During Control Period.—The patient was confined to bed and kept on a standard low-salt diet for a control period of two weeks. Digitalization was carried out on the first hospital day and was maintained thereafter. Ten separate injections of Mercuhydrin (2 ml. each) were given during the control period, but they failed to change the patient's condition. Slight temporary relief was afforded by the removal of 1,300 ml. of pleural fluid; nevertheless, orthopnea, cyanosis, and massive anasarca were still essentially unchanged on the fourteenth hospital day. At this time, the venous pressure was 11 cm. of saline, circulation time 24 seconds (arm to tongue), plasma sodium concentration 156 meq. per liter, potassium 5.1 meq. per liter, chloride 97.5 meq. per liter, blood nonprotein nitrogen 49 mg. per cent, serum albumin 2.72 Gm. per cent, and serum globulin 4.94 Gm. per cent.

Course During 50 mg. Sodium Regimen.—The patient was placed on the 50 mg. sodium diet for thirteen days. No diuretics were given. Digitalis was continued in the same dosage, and the electrocardiographic signs of digitalization remained the same as in the latter part of the control period. The patient improved remarkably under this regimen, and pulmonary râles and peripheral edema disappeared completely. The weight decreased from 62.00 kg. to 49.32 kg. The venous pressure fell from 11.8 cm. to 5.0 cm. Circulation time increased paradoxically from 24 to 30 seconds. Roentgenograms of the chest showed marked clearing of the congestion, as illustrated in Fig. 1.

TABLE II.

	J. T.	M. F.		K. B.	K. W.	L. C.	J. D.	M. W.
No. Days	13	6	6	16	9	10	8	9
Weight (kg.)								
Initial	62.00	60.00	58.40	66.12	50.00	68.70	85.18	75.64
Final	49.32	58.40	60.10	57.45	48.00	67.41	71.45	67.49
Difference	− 12.68	− 1.60	+ 1.70	− 8.67	− 2.00	− 1.29	− 13.73	− 8.15
Water (L.)								
Total	− 10.15	− 2.13	+ 0.85	− 8.67	− 1.92	− 1.16	− 14.16	− 8.15
Extracellular	− 9.15	− 1.90	− 0.20	− 5.78	− 1.30	− 0.72	− 12.21	− 6.00
Intracellular	− 1.00	− 0.23	+ 1.05	− 2.89	− 0.62	− 0.44	− 1.95	− 2.15
Total Chloride (meq.)	− 926	− 13.8	− 11.6	− 620.6	− 6.2	0	−1260	− 489.1
Sodium (meq.)								
Total	−1227	− 101	− 69	− 910	− 164	+ 4	−1545	− 595
Extracellular	−1420	− 300	− 40	−1025	− 130	− 200	−1930	− 900
Intracellular	+ 193	+ 199	− 29	+ 115	− 34	+ 204	+ 385	+ 305
Potassium (meq.)								
Total	+ 468	+ 349.5	+ 287.6	+ 297	+ 327	+ 115.6	+ 108.3	+ 48.2
Extracellular	− 47	− 10.3	+ 15.8	− 23	− 6.6	− 3.6	− 48.2	− 25.0
Intracellular apparent	+ 515	+ 359.8	+ 271.8	+ 321	+ 333.6	+ 119.2	+ 156.5	+ 73.2
Due to protein	+ 60.6	+ 18.0	+ 59.7	+ 17.4	+ 101.7	+ 21.6	− 64.8	+ 11.1
Intracellular real	+ 454.4	+ 341.8	+ 212.1	+ 303.6	+ 231.8	+ 97.6	+ 221.3	+ 62.1
Nitrogen (Gm.)								
Total	+ 14.9	+ 7.3	+ 21.9	− 2.5	+ 27.5	+ 3.0	− 26.6	+ 7.5
Body NPN	− 5.3	+ 1.3	+ 2.0	− 8.3	− 6.4	− 4.2	− 5.0	+ 3.8
True nitrogen	+ 20.2	+ 6.0	+ 19.9	+ 5.8	+ 33.9	+ 7.2	− 21.6	+ 3.7
Plasma (meq. per liter)								
Sodium								
Initial	156	147	145	165	143	153	155	160
Final	157	145	144	160	150	146	151.6	164
Potassium								
Initial	5.1	4.3	4.1	4.4	5.1	5.1	4.4	4.7
Final	5.1	4.1	5.5	4.6	5.1	5.1	4.7	5.0
Chloride								
Initial	97.5	78.5	89.3	102.0	79.8	99.9	102.8	91.4
Final	103.0	89.3	90.6	99.0	90.2	105.5	103.2	95.6
Blood NPN (mg. per cent)								
Initial	49	36	41	49	53	46	46	34
Final	48	41	45	39	37	38	49	48

Metabolic Studies.—The thirteen-day study was divided into four periods as follows: period I, comprising the first three days; II, including days four through six; III, including days seven through ten; IV, comprising the last three days. The total balances of water, sodium, potassium, chloride, and nitrogen for the entire thirteen days are given in Table II, and the cumulative balances for the duration of the study are represented graphically in Fig. 2. The scales for weight change and water balance in Fig. 2 are equivalent to each other. The scales for water balance and sodium balance are proportionate to the concentration of sodium normally found in extracellular water, i. e., 150 meq. of sodium per liter of water. The scales of potassium and nitrogen balances are roughly proportionate to the amount of potassium associated with protein in the cell, i. e., 3 meq. of potassium per gram of nitrogen. The total balance of water and sodium is represented by a solid line and the extracellular balance by a broken line. Intracellular balance is obtained by algebraic subtraction of extracellular balance from the total balance. A solid line is also employed for total potassium balance, but the broken line represents intracellular rather than extracellular balance.



Cumulative changes during recovery from congestive heart failure

Fig. 2.

Water, Chloride, and Sodium Balances.—A study of Fig. 2 reveals a progressive and a parallel decrease in body weight, total water, and sodium, the losses for the entire thirteen-day period amounting to 12,680 Gm., 10,147 ml., and 1,227 meq., respectively. The total loss of chloride for the same period was 926 meq. Since the plasma concentration rose from 97.5 meq. per liter at the beginning to 103 meq. per liter at the end of the study, it was apparent that relatively less chloride than water was lost from the extracellular space. Approximately 90 per cent (9,150 ml.) of the lost water came from extracellular sources, and this resulted in shrinkage of the extracellular

compartment to roughly one-half of its initial volume. The daily water elimination through insensible loss averaged 1,366 ml. and 1,360 ml. for periods I and II and decreased to 1,027 ml. in period III and to 832 ml. in period IV, presumably due in part to improvement in dyspnea.[7]

Sodium losses from the extracellular space amounted to 1,420 meq., of which 1,227 meq. (or 87 per cent of the total) were recovered in the excreta, the remaining 193 meq. (or 13 per cent) shifting into the cells. The plasma sodium concentration did not change, inasmuch as sodium and water were lost from the extracellular compartment in an average concentration of 155 meq. per liter, which was isotonic with the plasma. During the first period, the cells gained water and lost sodium, but thereafter the reverse took place, ending in an over-all negative intracellular water balance of 997 ml. and a positive intracellular sodium balance of 193 meq.

Nitrogen and Potassium Balance.—A positive nitrogen balance of 14.9 Gm. was found during the thirteen-day study, despite a proteinuria averaging 8.0 Gm. daily. Since calculations based on changes in body water and nonprotein nitrogen concentration revealed a loss of 5.3 Gm. stored nonprotein nitrogen, the retained nitrogen available for protein synthesis amounted to 20.2 Gm.

Potassium balance was strongly positive during each period, the total gain amounting to 468 meq. Plasma potassium was at a level of 5.1 meq. per liter at the beginning and end of the experimental period, but it fell to 3.33 meq. per liter in the midst of the study, perhaps because of the rapid cellular uptake. The cells actually gained 515 meq. of potassium, since the extracellular potassium decreased by 47 meq. as a result of profound shrinkage in this compartment. From the nitrogen balance, it would appear that a maximum of 60.6 meq. of the retained potassium could be accounted for by protein anabolism; the remaining 454.4 meq. presumably represented intracellular storage. Since cellular potassium concentrations do not rise above normal as long as the plasma level remains normal,[8] the uptake of 454.4 meq. represents a replenishment of a deficit existing when the patient was in congestive failure.

Thus, the loss of intracellular water, the marked gain in potassium, and the moderate gain in sodium during restoration of compensation lead one to the inference that the cells took up water but lost potassium and sodium during the development of congestive failure.

CASE 2.—M. F., a 42-year-old white man, was admitted on Sept. 7, 1949, in marked respiratory distress. He gave a history of increasing exertional and nocturnal dyspnea over a period of four years; he had been totally incapacitated for the past two years and had been hospitalized almost continuously for the last six months. Gross hemoptysis had occurred twice during this period. Moderate ankle edema was present on and off for one year. He was hospitalized elsewhere for the past two months, but he remained in congestive failure despite full digitalization. Within five days of discharge, dyspnea became so marked that he was admitted to Receiving Hospital.

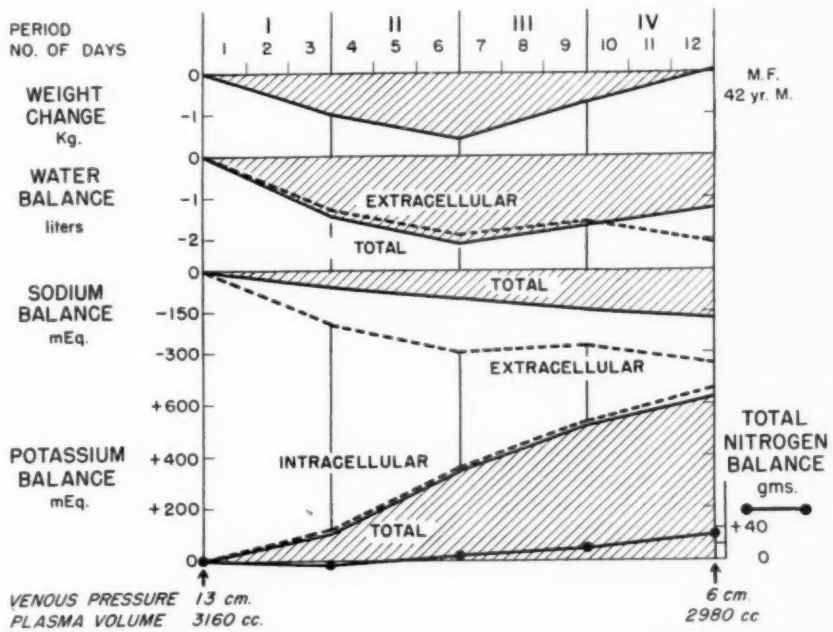
Physical Examination.—Marked orthopnea and cyanosis were revealed. The blood pressure was 100 mm. Hg systolic and 70 mm. Hg diastolic. Neck veins were distended. Rhonchi and crackling râles were heard throughout both lung fields, and marked congestion was found on roentgen examination. The left border of the heart was 10 cm. from the midline and the right border 4.5 cm.; the cardiothoracic ratio was 49 per cent. There was marked systolic lifting of the sternum referable to right ventricular hypertrophy. There was roentgenographic evidence of left atrial enlargement. The rhythm was grossly irregular. At the apex there was a loud rumbling murmur which extended throughout diastole and ended in a snapping first sound. The continuation of the murmur throughout long diastolic pauses indicated a severe grade of mitral stenosis. The pulmonary second sound was markedly accentuated. The liver extended 3 cm. below the right costal margin, but was not tender. Pressure over the liver produced a reflex cough. The left leg was amputated below the knee. There was no edema of the sacrum or right leg.

Laboratory Studies.—These showed blood hemoglobin of 12 Gm. per cent and a negative urinalysis. The blood urea nitrogen was 10 mg. per cent. The electrocardiogram showed auricular fibrillation, right ventricular hypertrophy, and full digitalization.

Course During Control Period.—The patient was placed on a 400 mg. sodium intake for a period of ten days. During this interval he was confined to bed and received oxygen intermittently. Full digitalization was established and maintained. Aminophylline was given intravenously three times daily, and Mercuhydrin was administered every other day in doses of 2 ml.

In spite of this regimen for ten days, no improvement occurred. Pulmonary congestion and nightly episodes of pulmonary edema continued unabated. The neck vein distention did not change. On Sept. 17, 1949, the venous pressure was 13.3 cm., vital capacity 1,700 c.c., and plasma volume 3,160 c.c. Plasma levels were as follows: sodium 147 meq. per liter, potassium 4.3 meq. per liter, and chloride 78.5 meq. per liter.

Course During 50 mg. Sodium Regimen.—This was instituted on Sept. 19, 1949, and continued until October 2; metabolic studies were carried out during the last twelve days. Digitalis was continued in the same maintenance dosage, and the electrocardiographic signs of digitalis action showed no change. Mercuhydrin was given every two to three days. The studies were divided into four periods of three days each. Objective measurements of cardiac compensation were repeated at the end of the twelfth day.



Cumulative changes during recovery from congestive heart failure

Fig. 3.

Symptomatically and objectively, the patient improved under this regimen. Pulmonary congestion decreased and attacks of pulmonary edema ceased. Cyanosis cleared, and the neck vein distention disappeared by the sixth day. Venous pressure fell to 6.5 cm. on the seventh day and then to 5.8 cm. on the twelfth day. Vital capacity increased to 2,200 ml., and the plasma volume fell to 2,980 ml. The weight fell from 60 to 58.40 kg. in six days and then rose to 60.10 kg. without any evidence of reaccumulation of pulmonary edema.

After fourteen days a 200 mg. sodium diet was substituted. The patient continued to improve to the point where mitral valve commissurotomy was performed successfully four weeks later. A severe degree of stenosis of the mitral valve was found at operation. After the operation, the tolerance to activity improved moderately.

Water, Chloride, and Sodium Balance.—A study of Fig. 3 reveals a progressive weight loss and parallel water loss during the first six days and a weight gain together with water retention during the last six days. Insensible loss of water for the first six days was 1,030 ml. per day and for the second six days 1,055 ml. per day. Nearly 90 per cent of the 2,130 ml. of water lost during the

first six days came from the extracellular compartment and was accompanied by a proportionate loss of extracellular sodium, as indicated by a constant plasma sodium level. Two-thirds of the 300 meq. of sodium leaving the extracellular compartment shifted into the cells and apparently must have caused a significant rise in intracellular concentration in view of the slightly negative intracellular water balance. This may have reflected correction of an intracellular deficit and/or compensation for hypochloremic alkalosis consequent upon the long-continued use of mercurials.[9] Concomitant chloride balance was only slightly negative, permitting a rise in plasma concentration from 78.5 meq. per liter at the beginning to 89.3 meq. per liter at the end of the first six days.

The weight gain of 1,700 Gm. during the last six days was not due to either pulmonary or peripheral edema, as suggested by the progressive clinical improvement and verified by a negative extracellular water balance of 200 ml. The constancy of plasma sodium concentration indicated a proportionate loss of extracellular sodium. The cellular uptake of water and potassium was accompanied by a loss of 29.2 meq. of sodium. The displacement of sodium by potassium may have represented a correction of a previous excess intracellular sodium, secondary to hypochloremic alkalosis and/or potassium deficit from other causes.

Nitrogen and Potassium Balance.—A slightly positive nitrogen balance of 7.3 Gm. was found during the first six days and a more markedly positive balance of 21.9 Gm. was found during the last six days. The retained nitrogen was apparently stored as protein, since the blood nonprotein nitrogen concentration did not change appreciably. After corrections for fluctuation in nonprotein nitrogen balance, the true metabolic nitrogen balance was +6.0 and +19.9 Gm. for the first six and second six days, respectively.

Strongly positive intracellular balances of potassium were found, not only during the first six days while extensive pulmonary edema was being removed, but also during the last six days when compensation was being maintained. The intracellular uptake of potassium was 359.8 meq. during the first half of the study and 271.8 meq. during the last half. After deduction of the portion of the retained potassium that might have been utilized for protein synthesis, cellular gains of potassium amounted to 341.8 meq. and 212.1 meq. for the respective halves of the study. The uptake of 553.9 meq. of potassium over and above that required for protein anabolism presumably represented a replenishment of a deficit accompanying congestive failure.

Although passive congestion was confined largely to the lungs in this patient, the potassium deficit appeared to be even greater than in the first patient, in whom there was massive anasarca. Furthermore, restriction of sodium intake and replenishment of potassium deficit were accompanied by a decrease in pulmonary congestion and edema and clinical improvement as dramatic as in Case 1.

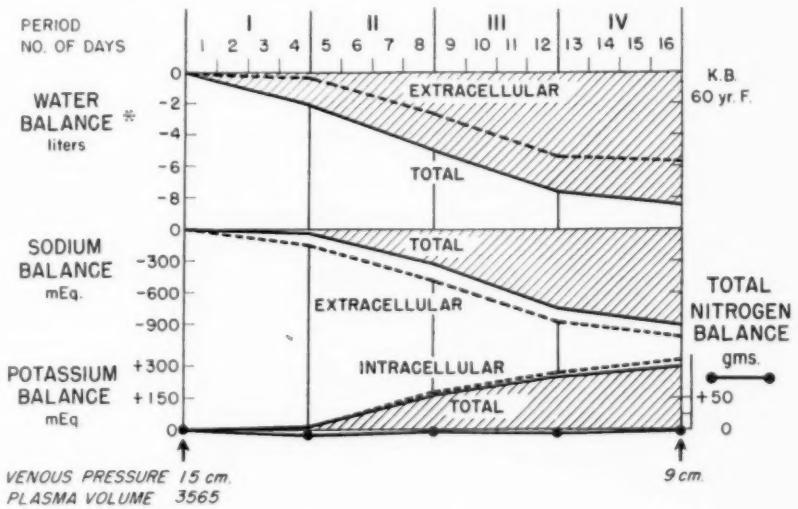
CASE 3.—K. B., a 62-year-old, white female patient, was admitted to the hospital on Dec. 14, 1949, in congestive failure. Hypertension was discovered three years prior to admission, and cardiac failure with dyspnea and dependent edema developed one year later. The patient was maintained in partial compensation by means of low-sodium diet, digitalis, and frequent mercurial injections until one month prior to admission, when she became refractory to treatment.

Physical Examination.—A markedly dyspneic and cyanotic elderly woman was revealed. The blood pressure was 180 mm. Hg systolic and 120 mm. Hg diastolic. The retinas showed grade 2 hypertensive changes. Cheilosis was present on the corners of the mouth. Cervical veins were distended. Physical and roentgen examination of the chest revealed marked pulmonary congestion and edema. The left border of the heart was 10 cm. from the midline and the right border 7 cm.; the cardiothoracic ratio was 72 per cent. The rhythm was grossly irregular, and a protodiastolic rumbling murmur was heard at the apex. The liver extended 3 cm. below the right costal margin. Marked edema was present over the sacrum and lower extremities.

Laboratory Studies.—These indicated a blood hemoglobin concentration of 14 Gm. per cent, a 3 plus albuminuria, and a urinary specific gravity of 1.024. Serum albumin was 3.77 Gm. per cent, and globulin was 2.51 Gm. per cent. Blood urea concentration was 16 mg. per cent. The electrocardiogram showed auricular fibrillation, left bundle branch block, and digitalis effect.

The venous pressure was 15 cm. of saline, and arm-to-tongue circulation time was 35 seconds. Plasma volume was 3,565 ml., the approximate normal for the patient being 2,150 ml.

Course on 50 mg. Sodium Regimen.—Since the patient was in severe grade 4 failure in spite of intensive treatment at home, she was immediately placed on the special 50 mg. sodium diet. Because of increasing apathy, lethargy, and weakness during the first twenty-four hours, together with the history of refractoriness to mercurial diuretics at home, hypochloremia and hyponatremia were suspected. Accordingly, 200 ml. of normal saline with 10 ml. of concentrated Hartmann's solution were given slowly by the intravenous route on the second day, but they produced no change in the clinical condition. The suspicion proved to be unfounded, since the plasma sample taken before the administration of the saline showed a chloride concentration of 102 meq. per liter and a sodium concentration of 165 meq. per liter. The 50 mg. sodium diet was given for sixteen days without further sodium supplements. Mercuhydrin was given in doses of 1 ml. on the second, fifth, and eighth days. Digitoxin was given in doses of 0.2 mg. daily for seven days and 0.1 mg. daily thereafter. Digitalis effect remained the same on the electrocardiogram. The patient was in critical condition for the first two days and then showed gradual progressive improvement. She required oxygen by nasal catheter until the tenth hospital day when cyanosis had disappeared. Dyspnea and pulmonary râles had cleared completely by the end of the study, and peripheral edema had decreased markedly. Weight declined from 66.12 to 57.45 kg. in sixteen days, and venous pressure fell to 9 cm. of saline. Improvement continued on a 200 mg. sodium intake, and the weight stabilized at 52.0 kg. on the thirty-third day.



Cumulative changes during recovery from congestive heart failure

* Total water balance derived from weight change

Fig. 4.

Water, Chloride, and Sodium Balance.—Total water balance was derived from the weight change, since insensible loss of water was not determined in this patient. Fig. 4 shows progressive decrease in total water and sodium, amounting to 8,670 ml. and 910 meq., respectively. Total loss of chloride during the sixteen days of study was 620.6 meq. Plasma chloride concentrations changed only slightly, indicating that water was lost from the extracellular space in amounts proportionate to chloride. Extracellular water loss of 5,780 ml. represented 67 per cent of the total loss. The remaining 33 per cent or 2,890 ml. was, therefore, lost from the cells. As shown in the graph (Fig. 4), most of this loss of intracellular water took place during period I, at which time extracellular water loss was practically zero.

The edematous extracellular compartment lost 1,025 meq. of sodium, of which 910 meq. (89 per cent) were eliminated from the body and 115 meq. (11 per cent) were transferred into the cells. This intracellular shift occurred entirely during period I. The plasma sodium concentration was unusually high on admission and remained at a plateau between 165 and 160 meq. per liter during the sixteen-day period, despite the low sodium intake. Hence, sodium disappeared from the extracellular compartment in concentrations approximately isotonic with plasma. This is shown graphically by the parallel slopes of the extracellular water and extracellular sodium lines. The high sodium and normal chloride concentrations suggested bicarbonate retention and possible alkalosis as factors in the relatively slow restoration of compensation, but unfortunately the bicarbonate and pH were not determined. Plasma sodium level remained elevated in the vicinity of 160 meq. per liter for four weeks after termination of balance studies, then it dropped to 152 meq. per liter. Plasma potassium levels were normal throughout, and no clinical evidence of Cushing's syndrome was present.

Nitrogen and Potassium Balance.—Nitrogen balance was slightly negative (2.5 Gm.) for the sixteen-day period. Since the blood nonprotein nitrogen level fell from 49 to 39 mg. per cent and total body water decreased from 48.88 to 40.21 kg.,* a total of 8.3 Gm. of nonprotein nitrogen was lost from the body, leaving a net tissue gain of 5.8 Gm. of nitrogen available for protein synthesis.

A total of 321 meq. of potassium was gained by the cells in the sixteen-day period. Since a maximum of 17.4 meq. could have been diverted to protein synthesis, 303.6 meq. were stored, presumably to replenish a deficit accompanying congestive failure.

During the first period when the clinical condition was critical, potassium uptake was very small, amounting to only 14.8 meq. During the second period the potassium uptake was ten times as great as in the first period and was more comparable to that in the two preceding patients. The small potassium retention during the first period could be attributed to several factors, including the critical condition of the patient, the associated anorexia leading to an average intake of only 56 meq. of potassium daily out of the 108 meq. supplied by the full diet, and the concomitant cellular uptake of 125 meq. of sodium, possibly for the purpose of compensating against alkalosis.

CASE 4.—K. W., a 60-year-old Negro woman, was originally admitted to the gynecological wards on June 5, 1949, because of a large ovarian tumor which was causing recurrent abdominal pain. Hypertension had been present for at least three years, and cardiac failure with dyspnea on exertion, orthopnea, and recurrent ankle edema had been present for two years. During a five-week period on the gynecological wards, the roentgenographic shadow of the heart widened perceptibly, pulmonary congestion and edema increased, but no evidence of pulmonary infarction was demonstrated. She was accordingly transferred to the medical service on July 12.

Physical Examination.—After transfer examination revealed orthopnea and cyanosis. The blood pressure was 260 mm. Hg systolic and 140 mm. Hg diastolic. There was glaucomatous optic atrophy on the right and papilledema on the left. The retinal arterioles on the left showed grade 2 narrowing and sclerosis. Few small, hard white exudates were seen in both eyes. The cervical veins were distended and exhibited a positive venous pulse. Physical and roentgen examination of the chest showed marked pulmonary congestion and edema. The left border extended 11.5 cm. from the midline and the right border, 7.5 cm.; the cardiothoracic ratio was 73 per cent. A forceful apical impulse was felt in the left anterior axillary line, and systolic lifting of the sternum was found and attributed to right ventricular hypertrophy, secondary to left-sided failure. A protodiastolic gallop was present at the apex. The liver reached 4 cm. below the costal margin. A large, firm cystic mass of ovarian origin occupied most of the lower half of the abdomen. There was a grade 2 edema of the sacrum and the lower extremities.

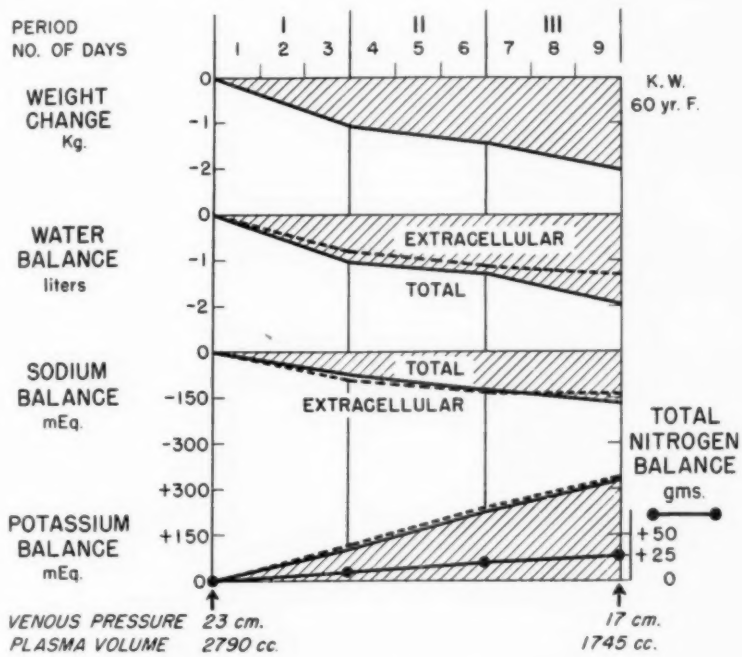
Laboratory Examinations.—These showed a blood hemoglobin concentration of 12.5 Gm. per cent and an albuminuria of 1 plus. Blood urea nitrogen was 17 mg. per cent, and the maximum urea clearance was 88 ml. per minute. Glomerular filtration rate (mannitol), corrected to

*The figure of 40.21 kg. represented 70 per cent of the body weight at the end of the study; the figure of 48.88 kg. was obtained by adding total water loss during the period. Calculations were based on the premise that nonprotein nitrogen was equally distributed through the body water.

1.73 sq. M., was 82 ml. per minute, renal plasma flow (PAH) was 241 ml. per minute, and the maximum tubular excretory capacity for PAH was 57.2 mg. per minute. The venous pressure was 26.0 cm. of saline, and the arm-to-tongue circulation time was 34 seconds. Intravenous pyelogram showed indentation of the ureters by the ovarian tumor.

Course During Control Period.—The patient was treated on a low-salt diet, thrice weekly mercurial injections, and maintenance doses of digitalis for seven weeks. Peripheral edema decreased considerably, as reflected in a weight loss of 2.6 kg.; however, pulmonary congestion persisted and orthopnea failed to improve. Venous pressure remained elevated at 23 cm. of saline, and circulation time fell only slightly to 28 seconds. The plasma volume at the end of the control period was 2,790 ml. or 800 ml. over the estimated normal. Plasma sodium was 143 meq. per liter, potassium 5.1 meq. per liter, and chloride 79.8 meq. per liter.

Course During 50 mg. Sodium Regimen.—This was given for nine days, during which time digitalis was continued in the same dosage, but mercurial injections were withheld. During this interval there was marked improvement in the clinical status as well as in the objective findings. Orthopnea was relieved, and râles were no longer audible. Peripheral edema disappeared, and weight fell from 50.0 to 48.0 kg. Venous pressure fell from 23 to 17 cm. Circulation time decreased from 26 to 15 seconds. Plasma volume fell 37.5 per cent from 2,790 to 1,745 c.c. The blood pressure remained elevated to 240 mm. Hg systolic and 140 mm. Hg diastolic.



Cumulative changes during recovery from congestive heart failure

Fig. 5.

A 200 mg. sodium diet was then substituted, and the patient remained compensated. A large ovarian cystadenoma was removed surgically without any complication. She has been followed for over one year in the outpatient department, and cardiac status has remained in Class II.

Water, Chloride, and Sodium Balance.—A weight loss of 2.0 kg., together with comparable negative water and sodium balances of 1,915 ml. and 164.1 meq., respectively, occurred during the

nine-day period of study. The average insensible loss of water was 1,739 ml. per day. Chloride loss was only 6.2 meq. for the same period. Since the plasma chloride concentration rose from 79.8 meq. per liter at the beginning to 90.2 meq. per liter at the end of the period, it was apparent that loss of chloride was small in proportion to loss of water from the extracellular compartment. Of this total water loss, 1,300 ml. (68 per cent) came out from the extracellular space and 615 ml. (32 per cent) from the intracellular space.

The plasma sodium level rose from 143 to 150 meq. per liter, indicating that the fluid lost from the extracellular compartment was slightly hypotonic in respect to sodium. The intracellular compartment lost 34.1 meq. of sodium during the period of study. This was the sole patient among the seven studied who showed a negative intracellular sodium balance during recovery from congestive heart failure.

Nitrogen and Potassium Balance.—Nitrogen balance was quite favorable in this patient, the total retention amounting to 27.5 Gm. in nine days. Assuming that the nonprotein nitrogen was distributed equally in body water, a fall in blood nonprotein nitrogen from 53 to 37 mg. per cent and a decrease in total water by 2 L. would indicate that approximately 6.4 Gm. of previously retained nonprotein nitrogen were eliminated from the body. Thus, as much as 33.9 Gm. of nitrogen were actually gained by the tissues and presumably synthesized into protein.

The total potassium balance was +327 meq. for the nine-day period; the intracellular balance was 6.6 meq. greater as a result of transfer from the shrinking extracellular space. A maximum of 101.7 meq. of retained potassium was used in the synthesis of protein; the remaining 231.8 meq. were stored in the cells, presumably to make up a deficit which had existed despite a seven-week hospitalization on a diet believed adequate in potassium. The plasma potassium levels were identical at the beginning and end of the study and thus failed to reflect the metabolic changes.

CASE 5.—L. C., a 31-year-old white man, was admitted because of gross hemoptysis. Rheumatic fever had developed at the age of 9 years and chorea at 13 years. He gave a history of increasing exertional dyspnea since the age of 25 years. During the last three years, he had several episodes of gross hemoptysis, two of which were sufficiently severe to require hospitalization. The femoral veins were ligated in 1948. The present hospitalization on Dec. 27, 1949 was preceded by three days of gross hemoptysis, the blood loss on the day of admission totalling approximately 300 ml.

Physical Examination.—On admission the patient was dyspneic and was coughing up moderate amounts of bright red blood. The temperature was 99.4° F. The blood pressure was 130 mm. Hg systolic and 60 mm. Hg diastolic. Physical and roentgen examination of the chest showed marked passive congestion but no evidence of pulmonary infarction. The left border of the heart extended 15 cm. from the midline and the right border, 6.5 cm.; the cardiothoracic ratio was 68 per cent. There was marked enlargement of the left atrium, causing esophageal displacement. There was heaving of the sternum from right ventricular hypertrophy and an abnormally prominent systolic pulsation in the left third interspace from dilatation of the conus pulmonalis. The rhythm was grossly irregular. Auscultatory findings were indicative of rheumatic mitral stenosis and regurgitation and aortic insufficiency. The liver extended 2 cm. below the costal margin. There was no peripheral edema. Slight clubbing of the fingers was present.

Laboratory Studies.—These showed a blood hemoglobin of 13.0 Gm. per cent and a negative urinalysis. Blood urea nitrogen was 17 mg. per cent. The vital capacity was 2.1 L., the circulation time 30 seconds, and the venous pressure 6 cm. of saline. Body weight was 68.72 kg. The electrocardiogram revealed auricular fibrillation and a late R′ deflection of high voltage in leads in the third and second interspaces near the left sternal border, attributed to hypertrophy of the conus pulmonalis.

Course During Control Period.—The patient was confined to bed and sedated with morphine and barbiturates. A low-sodium diet was administered. Digitalis was continued at maintenance levels and mercurial injections were given every other day. In spite of this regimen, dyspnea was unabated, and gross hemoptysis recurred twice during the next eight days. Because of the quantity of blood lost and the failure to demonstrate pulmonary infarction, the hemoptyses were attributed to repeated rupture of distended bronchial varices.[10]

A complete check, made nine days after admission, showed that vital capacity was still decreased at 2.1 L., and circulation time was still elevated to 28 seconds. Weight remained about the same, at 68.695 kg. Râles were now present in the right base as well as in the left. A roentgenogram showed the same degree of congestion in the lungs but no evidence of pulmonary infarction. Plasma sodium concentration was 153 meq. per liter, potassium 5.1 meq. per liter, and chloride 99.9 meq. per liter.

Course During 50 mg. Sodium Regimen.—This was instituted in an effort to reduce pulmonary congestion and to thereby lessen the danger of further bleeding from ruptured vessels. Digitalis was continued in the same dosage. Its effect remained the same on the electrocardiogram. No diuretics were given. During the course of a ten-day period on this diet, dyspnea cleared up, hemoptysis ceased, pulmonary râles disappeared, and the roentgenogram showed marked reduction in pulmonary congestion. There was a weight loss of 1.29 kg. and a 52 per cent increase in vital capacity from 2.1 to 3.2 L. Plasma volume on the sixth day of study was normal at 2,600 ml. A roentgenogram of the chest at the end of the study showed a slight reduction in heart size (cardiothoracic ratio 64 per cent) and only a minimal degree of pulmonary congestion. The patient improved sufficiently to become a good operative risk, but he refused mitral commissurotomy.

Water, Chloride, and Sodium Balance Studies.—These were carried out for a total of ten days and were divided into three periods of three, three, and four days' duration. Insensible loss of water averaged 1,400 ml. per day. A total negative water balance of 1,164 ml. corresponded closely to the weight loss of 1.29 kg. The extracellular compartment lost 720 ml. or 62 per cent of the total water, and the cells lost 444 ml. or 38 per cent. The slight rise in plasma chloride concentration from 99.9 meq. per liter to 105.5 meq. per liter was due exclusively to loss of water from the extracellular space, since the chloride balance was zero. External balance of sodium was also in equilibrium. Nevertheless, there was an internal shift of 200 meq. of sodium from the extracellular compartment into the cells. This quantity was proportionally greater than the amount of water removed from the extracellular space, as indicated by a slight fall in plasma sodium concentration from 153 meq. per liter to 146 meq. per liter.

Nitrogen and Potassium Balance.—Although nitrogen balance was slightly negative during period I, the over-all balance for the ten days was plus 3.0 Gm. Since the blood nonprotein nitrogen fell from 46 to 38 mg. per cent and since total body water decreased, the actual gain of tissue nitrogen was 7.2 Gm.

Plasma potassium concentration was kept constant at 5.1 meq. per liter due to transfer of 3.6 meq. from the shrinking extracellular compartment into the cells. There was an intracellular gain of 119.2 meq. of potassium of which 21.6 meq. could be related to protein synthesis, the remainder to storage in replacement of a deficit.

The magnitude of extracellular water and sodium loss was not great. This was to be expected in this patient, since no edema was clinically detectable prior to therapy. The disproportionate degree of pulmonary congestion was, no doubt, due to "pressure-flow" disturbance,[11] brought on by the mechanical obstruction at the stenotic mitral orifice. The small decrease in extracellular and plasma volumes was apparently sufficient to reduce the pulmonary hypertension, which was causing recurrent episodes of hemoptysis.

CASE 6.—J. D., a 65-year-old white man, was admitted to the hospital in marked congestive failure. Six months prior to admission, the patient began to have shortness of breath on exertion. Two months later he was hospitalized elsewhere for acute retention of urine, and a transurethral prostatic resection was performed. Progressive congestive failure developed after ambulation, despite full digitalization, and necessitated admission to the Receiving Hospital on April 18, 1950.

Physical Examination.—Orthopnea and cyanosis were revealed. Blood pressure was 190 mm. Hg systolic and 90 mm. Hg diastolic. Fundi showed retinal arteriolar narrowing and sclerosis of grade 2. Neck veins were slightly distended. Physical and roentgen examination revealed severe pulmonary congestion. The left border of the heart was 13 cm. from the midline and the right border, 7 cm; the cardiothoracic ratio was 72 per cent. The sounds were of poor quality and totally irregular. No murmurs were heard. The liver extended 8 cm. below the costal margin. There was 4 plus edema of the lower extremities and the back.

Laboratory Studies.—The blood hemoglobin concentration was 11.0 Gm. per cent. The urine showed a 3 plus albumin and 50 white blood cells per high-power field. Total plasma protein was 5.61 Gm. per cent with 3.17 Gm. of albumin and 2.44 Gm. of globulin. Blood urea nitrogen was 23 mg. per cent. The electrocardiogram showed auricular fibrillation and right bundle branch block. Numerous ventricular extrasystoles were also present. The venous pressure was 11 cm. of saline; the circulation time was 35 seconds from arm to tongue. The plasma volume was 4,260 c.c. and the hematocrit 43 per cent. Initial plasma sodium concentration was 155 meq. per liter, potassium 4.4 meq. per liter, and chloride 102.8 meq. per liter.

Course During 50 mg. Sodium Regimen.—This regimen was started on the second hospital day and was continued for eight days. During this interval, the patient received one intramuscular injection of 1 ml. of Mercuhydrin. Digitoxin was continued in maintenance doses. Its effect on electrocardiographic tracings remained constant. Prompt clinical improvement occurred. Dyspnea subsided, and pulmonary and peripheral edema disappeared within eight days. The venous pressure fell to 5.0 cm. of saline, and the circulation time decreased to 28 seconds. Vital capacity was not determined at the onset of study, but it was found to be 2,700 ml. on the ninth day and 3,300 ml. on the seventeenth day. The plasma volume decreased by 47 per cent from 4,260 ml. to 2,235 ml. A roentgenogram of the chest after eight days of 50 mg. sodium diet showed a decrease in pulmonary congestion from grade 4 to grade 1. The cardiothoracic ratio decreased from 72 to 65 per cent. The eight-day metabolic study was divided into two periods of four days each.

Water, Chloride, and Sodium Balances.—A weight decrease of 13.73 kg. and a total water balance of −14,160 ml. reflected an error inherent in this type of study, even when care is taken in weighings. Insensible loss averaged 1,400 ml. per day during period I and 1,375 ml. per day during period II. The extracellular compartment lost 12,210 ml. of water (or approximately 87 per cent of the total) and shrank to about 55 per cent of its original volume. The cells lost 1,950 ml. (or 13 per cent of the total). Since plasma chloride level was 102.8 meq. per liter at the beginning and 103.2 meq. per liter at the end of the study, chloride and water must have been removed from the extracellular compartment in isotonic concentrations. Thus, 1,260 meq. of chloride lost from the body and 12,210 ml. of water lost from the extracellular space represented a chloride concentration of 103 meq. per liter.

The extracellular compartment lost 1,930 meq. of sodium, of which 1,545 meq. (80 per cent) left the body and 385 meq. (20 per cent) shifted into the cells. The transference of sodium into the cells occurred exclusively during period I. The plasma sodium concentrations fell only slightly to 151.6 meq. per liter, indicating removal of fluid and sodium from the extracellular space in approximately isotonic proportion.

Nitrogen and Potassium Balance.—A negative nitrogen balance of 26.6 Gm. was observed in this patient and was attributable to a severe proteinuria, which averaged 18 Gm. daily. Shrinkage of the total water volume accounted for loss of 5 Gm. of nitrogen. Thus, the actual nitrogen loss from the tissues was 21.6 Gm. in eight days.

Total potassium gained by the body as a whole was 108.3 meq. An additional 48.2 meq. were transferred from the contracting extracellular space into the cells. Furthermore, an estimated 64.8 meq. of potassium were liberated by protein catabolism and were picked up by intact cells. Thus, the intracellular gain amounted to 221.3 meq. of potassium, or more than twice the external balance. This cellular uptake probably represented a replenishment of a deficit incurred during congestive failure.

CASE 7.—M. W., a 24-year-old white man, was admitted to the hospital on March 13, 1950 in severe right-sided cardiac failure. He had had rheumatic fever at the age of 12 years. He gave a history of recurrent dyspnea and dependent edema for the last eight years. He had been hospitalized because of congestive failure in 1946, 1947, and 1948, because of systemic embolism in 1948, and with thrombophlebitis of the right leg in 1949. Despite a low salt intake, digitalization, ammonium chloride, and triweekly injections of Mercuhydrin, dependent edema progressively increased over a two-month period and led to hospitalization.

Physical Examination.—Examination showed slight dyspnea, but marked edema of the lower extremities, back, and scrotum. Blood pressure was 120 mm. Hg systolic and 60 mm. Hg diastolic.

Physical and roentgen examination showed slight pulmonary congestion. The left cardiac border was 13.0 cm. from the midline and the right border, 8.0 cm.; the cardiothoracic ratio was 64 per cent. The rhythm was grossly irregular. Auscultatory findings were typical of mitral stenosis and insufficiency and rheumatic aortic insufficiency. The liver extended 3 cm. below the costal margin. Body weight was 75.74 kg.

Laboratory Studies.—Urinalysis was negative. Serum albumin was 3.16 Gm. per cent and globulin 1.91 Gm. per cent. Plasma carbon dioxide combining power was 33 volumes per cent. Plasma sodium concentration was 160 meq. per liter, plasma potassium 4.74 meq. per liter, and plasma chloride 91.4 meq. per liter.

The venous pressure was 11 cm. of saline, vital capacity 1,700 ml., circulation time 18 seconds, and plasma volume 5,270 ml. The electrocardiogram showed auricular fibrillation, left ventricular hypertrophy, and full digitalization.

Course on 50 mg. Sodium Diet.—This diet was instituted on the first hospital day. Digitalis was continued in doses of 0.1 Gm. daily. Electrocardiographic signs of digitalization remained the same at the beginning and end of the study. No mercurials were given. Metabolic studies were conducted for nine days and were divided into two periods of four and five days, respectively. During this interval the edema disappeared almost completely, and the lungs became clear of râles. Vital capacity increased to 2,500 ml., venous pressure fell to 8.8 cm., and the plasma volume decreased 54 per cent to 2,280 ml.

Water, Chloride, and Sodium Balances.—During the nine-day period of study, there was a decline in weight of 8.15 kg., a sodium loss of 595 meq., and a chloride loss of 489 meq. Fall in weight was considered to represent loss in total water. Plasma chloride concentration rose slightly from 91.4 to 95.6 meq. per liter, thus indicating loss of water from the extracellular space in slight excess to loss of chloride. Extracellular water loss was 6.00 L. (or 74 per cent of total), and the intracellular water loss was 2.15 L. (or 26 per cent of total). Plasma sodium concentration was elevated to 160 meq. per liter at the beginning of the study and remained at a plateau, indicating a proportionate decrease of extracellular sodium and water. Of the 900 meq. of sodium lost from the extracellular space, 595 meq. (66 per cent) left the body and 305 meq. (34 per cent) shifted into the cells.

Nitrogen and Potassium Balances.—Positive nitrogen balance of 7.5 Gm. was maintained. Since the blood nonprotein nitrogen level increased from 34 mg. per cent to 48 mg. per cent, 3.8 Gm. nitrogen were retained as nonprotein nitrogen, leaving 3.7 Gm. for protein synthesis.

The external potassium balance of +48.2 meq. was the least positive in the seven patients. The cells gained an additional 25 meq. of potassium through transfer from the shrinking extracellular compartment. Approximately 11 meq. of the cellular uptake of potassium could have been utilized in protein synthesis; the remaining 62 meq. presumably represented a replenishment of a cellular deficit.

DISCUSSION

Clinical Status at the Onset of the Study.—The patients were divided into two groups from the standpoint of distribution of the edema at the onset of the study: Group I, consisting of four patients with marked passive congestion of both the systemic and pulmonary circuits (J. D., J. T., K. B., and M. W.), and Group II, consisting of three patients in whom pulmonary edema was marked, but peripheral edema was either slight (K. W.) or clinically undetectable (M. F. and L. C.). The congestive failure in four of the patients (L. C., M. F., J. T., and K. W.) had proved refractory to a standard regimen, consisting of bed rest, a low-sodium diet, digitalization, and mercurial diuretics, carried out in the hospital for periods of nine, ten, fourteen, and forty-nine days, respectively; the decompensation in two others (K. B. and M. W.) had become steadily worse on a comparable regimen carried out in the home; progressive failure had occurred at home in the remaining patient (J. D.) despite full digitalization.

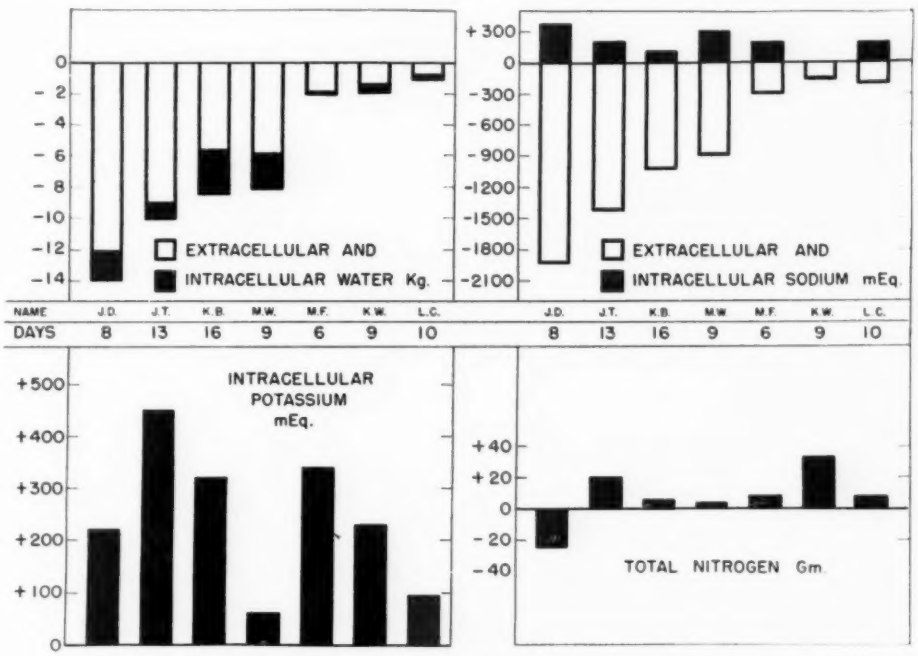
Clinical Changes During the Metabolic Study.—Progressive weight loss occurred in each patient and was referable to loss of water. Peripheral edema disappeared during the course of the study in three patients and decreased markedly in the other two. There was a striking decrease in pulmonary congestion and edema in every patient, manifested subjectively by relief of dyspnea, objectively by clearing of pulmonary râles and marked reduction or disappearance of roentgen signs. Improvement in pulmonary symptoms and signs was especially noteworthy in the two patients with marked mitral stenosis (M. F. and L. C.). There was a consistent fall in venous pressure and plasma volume and a rise in vital capacity in all patients in whom these determinations were made at the beginning and end of the experimental period.

The clinical improvement which occurred during the metabolic study could not be attributed to the digitalis given during the period since the glycoside was continued in the same maintenance doses employed in the control period. Mobilization of digitalis along with evacuation of edema could not have been a major factor in the improvement, since serial electrocardiograms showed no significant change in the degree of digitalis effect. Restoration of cardiac compensation took place despite withdrawal of mercurial diuretics in four of the patients and continuation of the same dosage in two others. It was, therefore, concluded that the recovery from congestive failure was attributable chiefly to the diet. The improvement resulted not only from the drastic restriction of sodium and moderate limitation of chloride, but probably also from the provision of liberal amounts of potassium and adequate water, protein, and calories. Nevertheless, these studies do not provide a rigid comparison of the 400 and 1,000 mg. sodium diets employed during the control period in the hospital with the 50 mg. diet given during the experimental period since the patients were on the open ward during the control period and might have taken additional sodium chloride surreptitiously.

Metabolic Studies.—These are summarized in Table II and in Fig. 6. The four charts which make up part of Fig. 6 show, in block form, the respective balances of water (intracellular and extracellular), sodium (intracellular and extracellular), intracellular potassium (after correction for that associated with protein metabolism), and intracellular nitrogen. The scales for sodium and water balance were made in a proportion of 150 meq. of sodium to 1 L. of water. The cases are arranged from left to right in the upper left hand chart in order of diminishing negativity of water balance, and the same sequence of case arrangement is maintained in the other three charts.

Water.—Total water loss was naturally much greater in the four patients with marked peripheral edema (J. D., J. T., K. B., and M. W.) than in the three patients with little or no peripheral edema (Fig. 6). In the first group, water loss ranged from 8,150 to 14,160 ml. and represented 11 to 17 per cent of the initial body weight; in the second group, it ranged from 1,160 to 2,130 ml. and represented 1.7 to 3.5 per cent of the initial weight. Most of the lost water came from the extracellular compartment, but a significant portion was derived from the cells. In the first group of patients, calculated intracellular water loss ranged from 997 to 2,890 ml. and comprised 10 to 33 per cent of the total water loss; in

the second group, intracellular water loss ranged from 230 to 615 ml. and comprised 11 to 38 per cent of the total loss. Since the proportion of intracellular water loss to total loss was comparable in the two groups, it is probable that changes in tissue tension had no bearing on shifts of water between the extracellular and intracellular compartments. It is noteworthy that shrinkage in the water content of the intracellular compartment occurred during recovery, despite a concomitant increase in cellular sodium and potassium and a positive nitrogen balance. The implications will be discussed after summary of sodium, nitrogen, and potassium balances.



Metabolic changes during recovery from congestive heart failure

Fig. 6.

Chloride.—The four patients with marked peripheral edema lost chloride from the body in large quantities (489 to 1,260 meq.). Initial and final plasma chloride concentrations were normal in two of these patients (J. D. and K. B.), indicating that water and chloride were evacuated from the extracellular compartment in isotonic proportions. Plasma chloride levels were slightly depressed at the beginning of the study in the other two patients of Group I (J. T. and M. W.) and rose during the course of the study and reached normal in J. T., indicating a relatively smaller loss of chloride than water.

In the three patients of Group II with little or no peripheral edema, chloride balance was either only slightly negative or in complete equilibrium. Plasma chloride concentration at the beginning of the study was depressed to 78.5 meq.

per liter in patient M. F. and to 79.8 meq. per liter in K. W., probably because of frequent mercurial injections during the control period. A sharp rise to 89.3 and 90.2 meq per liter, respectively, occurred in the two patients during periods of six and nine days on diets supplying only 36.97 meq. of chloride daily. These observations were demonstrative of the capacity of the kidneys to retain chloride preferentially over water in the presence of hypochloremia. Conservation of chloride was imperfect in these patients, however, since chloride balance was −13.8 and −6.2 meq., respectively. Plasma chloride concentration in the remaining patient rose from low normal value of 99.9 meq. per liter to high normal value of 105.5 meq. per liter while balance was in complete equilibrium.

Thus, diuresis of peripheral and pulmonary edema fluid during recovery under a diet containing 2.25 meq. of sodium and 36.97 meq. of chloride was attended by differential elimination of water and chloride in accordance with plasma chloride concentration.

Sodium.—External sodium balance was markedly negative in the four patients with extensive peripheral edema, ranging from −595 to −1,545 meq.; it was distinctly negative in two of the patients with little or no detectable peripheral edema, amounting to −101 and −164 meq., respectively, and was in equilibrium (+4) in the remaining case (L. C.). Plasma sodium concentration at the onset of the study was high in the four patients with marked peripheral edema (K. B., M. W., J. T., and J. D.), amounting to 165, 160, 156, and 155 meq. per liter, respectively. These findings are consistent with those cited by Cantarow and Trumper.[12] Furthermore, the values remained at approximately the same level in three of the patients during a nine to sixteen-day period on the extremely low sodium intake of 2.25 meq. and fell merely from 155 to 151.6 meq. per liter during an eight-day regimen in the other patient. The plasma sodium levels fluctuated within the usual normal range in the three patients with little or no peripheral edema and did not fall below our average normal value of 142 meq. per liter[13] in any patient. The maintenance of plasma sodium concentration at a plateau indicated that losses of extracellular sodium were consistently parallel to losses of extracellular water. This is illustrated in Figs. 2, 3, 4, and 5 and is also brought out by a comparison of the depths of the corresponding open blocks of the two upper charts of Fig. 6.

Losses of sodium from the extracellular compartment exceeded losses from the body in six of the seven patients, due to transfer of sodium into the cells. Intracellular sodium balance ranged from +115 to +385 meq. (average +249 meq.) in the four patients with marked peripheral edema and amounted to +199 and +204 meq. (average +201.5 meq.) in the two patients with no detectable peripheral edema. It was −34 meq. in the remaining patient (K. W.). There was no consistent relation between the quantity of sodium taken up by the cells and the magnitude of the sodium surplus present in or being evacuated from the interstitial space. Movements of sodium between extracellular and intracellular compartments were almost invariably opposite to movements of water during the first six to eight days of the study, but tended to become parallel after compensation was restored. The usual finding during the early stages of recovery from congestive failure was a transfer of sodium from the interstitial space into the

cells and a concomitant shift of water out of the cells. The cellular uptake of sodium probably did not represent a simple correction for alkalosis,[8] since under these circumstances one would have anticipated a displacement of potassium out of the cells, instead of the strongly positive intracellular balance actually observed in these patients. Moreover, the migration of sodium into the cells was not necessarily secondary to high plasma concentrations, since a positive intracellular sodium balance of 199 meq.was observed in one patient whose plasma sodium levels ranged between 147 and 144 meq. per liter. Sodium uptake by the cells was apparently independent of protein anabolism, since the patient with the most positive intracellular sodium balance had a negative nitrogen balance (J. D.). The cellular uptake of sodium and potassium and coincident release of water during recovery apparently represented a compensation for an abnormality in cellular water and electrolyte associated with congestive failure and will be discussed at more length later.

Nitrogen.—Balance was positive in five patients and was −2.5 Gm. in patient K. B. and −26.6 Gm. in J. D. Upon analysis of the cause of the negative nitrogen balance in J. D., it was found that 5.0 Gm. represented stored nonprotein nitrogen and the remaining 21.6 Gm. was lost through a proteinuria, which averaged 18 Gm. daily. The slightly negative balance in K. B. could be accounted for by the elimination of excess nonprotein nitrogen sufficient to reduce the plasma concentration from 49 to 39 mg. per cent. After correction for this factor, it was found that there was a net cellular gain of 5.8 Gm. of nitrogen. Correction of nitrogen balances in the other five patients for alterations in total nonprotein nitrogen content revealed net cellular gains of 3.7 Gm. to 33.9 Gm. of nitrogen available for protein synthesis. There was no apparent correlation between either the degree of failure at the onset of the study or the speed of recovery and the quantity of nitrogen stored (and presumably utilized) for protein anabolism.

Potassium.—Plasma concentrations at the beginning and end of the study were in close agreement in each of the seven patients, indicating that shrinkage of extracellular volume during recovery was accompanied by a proportionate reduction of total extracellular potassium. Since the external balance was positive in all patients, the potassium lost from the extracellular compartment was apparently taken up by the cells.

Intracellular potassium balance was positive in all patients, ranging from 73 meq. to 515 meq. The magnitude of the potassium uptake during recovery from congestive failure compared favorably with that found in one patient by Sinclair-Smith and co-workers.[14] Total cellular uptake of potassium undoubtedly would have been greater if determinations had been continued for longer periods, since potassium balance was still distinctly positive during the final days of the study in every patient. In fact, studies were continued for an additional six days after marked clinical improvement in patient M. F., and a positive intracellular balance of 271.8 meq. was found during this period, as compared with 359.8 meq. during the previous six days when pulmonary edema was being removed.

No significant correlation was found between the degree and type of failure at the beginning of the study and the quantity of potassium taken up by the

cells during recovery, as will be evident from a comparison of corresponding blocks in the upper and lower left hand charts of Fig. 6. This is also borne out by the calculated daily cellular uptake of potassium, which averaged 27.6, 34.9, 19.0, and 6.9 meq. for the four patients in Group I and averaged 56.9, 25.8, and 9.8 meq. for the three patients of Group II. There was no consistent relation between the cellular uptake of potassium and sodium. Cellular uptake of potassium continued throughout the study in all patients and proceeded at a remarkably uniform rate in three. It was slower at the beginning than it was later in the study in two patients and tapered off somewhat toward the end in two. On the other hand, intracellular sodium balance was most positive during the first or second period in all but one patient and tended to become slightly negative toward the end of the study. There was no correlation between the amount of water released by the cells and the amount of potassium retained.

The cellular uptake of potassium could be attributed, in part, to protein synthesis. After subtraction or addition of 3 meq. of potassium for each gram of nitrogen retained or lost by the cells, the calculated cellular uptakes of potassium for purposes other than protein anabolism amounted to 221.3, 454.4, 303.6, and 62.1 meq., respectively, for the four patients in Group I and 341.8, 231.8, and 97.6 meq. for the three patients in Group II. The above figures included potassium retained in glycogen synthesis, but the fraction so utilized was indeterminate from our data. The magnitude of the potassium uptake in five of the seven patients exceeded that to be expected from maximal glycogen synthesis,[15] utilizing the figure of 1 to 1.5 meq. of potassium per kilogram retained as a result of glycogenesis during recovery from diabetic coma.[8] Since glycogen depletion comparable to that in diabetic coma would not have been anticipated in this series, it is probable that all patients had positive intracellular balances of potassium over and above that utilized in protein and glycogen synthesis.

The markedly positive potassium balance accompanying recovery from congestive failure represented a correction of an intracellular deficit rather than a storage of supernormal quantities of potassium in the cells, since cellular concentrations of potassium do not exceed normal as long as plasma potassium levels remain normal.[8] Although digitalis reduces the potassium content of cardiac muscle, the depletion in these patients was not attributable to digitalis given before hospitalization or during the control period, inasmuch as the markedly positive intracellular balances of the experimental period occurred without change in digitalis dosage. Mercurials produce diuresis of potassium[9] and those given before hospitalization or during the control period may have contributed to the potassium loss; however, mercurials were not the major factor governing potassium shifts, since a markedly positive intracellular balance occurred in patient M. F. during recovery from pulmonary edema on the 50 mg. sodium regimen, despite continuation of Mercuhydrin in the same dosage as during the control period. Furthermore, patient J. D. received no mercurial prior to the onset of the study, but he showed a marked cellular uptake of potassium during recovery from congestive failure. The potassium depletion at the onset of the study was not attributable to excessive losses through the alimentary tract because of the absence of diarrhea and vomiting and was not referable to a potassium-losing

nephritis because of the prompt conservation of potassium during recovery. The potassium depletion in these patients differed from that secondary to alkalosis in that sodium as well as potassium was taken up by the cells during recovery.

The cellular depletion of potassium during congestive failure probably represented a primary alteration in cellular composition, rather than a secondary change compensatory to excessive excretion or to alteration in the composition of extracellular fluids. The factors which may have contributed to a cellular depletion of potassium during congestive failure include anoxia[17,18] and a possible stress reaction;[19] however, a quantitative evaluation of these factors is not possible from our data.

Interrelationships of Water and Electrolyte Metabolism During Recovery From Congestive Failure.—The extracellular compartment lost water and chloride in proportions that maintained an initially normal chloride concentration at a plateau, but raised an initially subnormal level to or toward normal. Hyperchloremia was not found in any of our patients. The extracellular compartment lost sodium in proportions which maintained the initial concentrations of sodium, irrespective of whether they were elevated or normal. Hyponatremia was not observed at any time during the course of this study; however, Fox, Friedberg, and White[20] found subnormal sodium levels in nineteen of twenty-six patients with congestive failure and noted a tendency toward a rise in plasma sodium concentration during recovery. The maintenance of plasma sodium and potassium concentrations approximately at a plateau in our patients indicated no significant change in osmolarity of the extracellular compartment.

During the patients' recovery from congestive failure, the intracellular compartment lost water, but gained potassium and sodium. These shifts were considered significant because of their consistency and magnitude. Furthermore, Miller,[21] in a study of electrolyte balance in eight patients recovering from congestive failure, demonstrated a consistent cellular uptake of both potassium and sodium.

If the cellular osmolarity in our patients had been increased by an amount equivalent to the gain of sodium and potassium plus the loss of water, the cells would have become distinctly hypertonic in respect to the extracellular fluid, which showed no significant change in osmolarity. Such a relationship is physiologically untenable. Therefore, conversion of cellular base from an osmotically active to an inactive form presumably took place parallel with the cellular uptake of electrolyte and loss of water. Rapid osmotic inactivation of cell base was demonstrated by Elkinton, Winkler, and Danowski[22] under conditions other than congestive heart failure. These authors further contended that such sodium and potassium shifts may be related to metabolic activity of the cell and energy exchange rather than to a mere passive transfer.[23]

The cellular uptake of nitrogen and potassium and loss of water during recovery from congestive failure were similar in direction to the changes that would have been expected with a return from adrenal cortical hyperactivity from the stress reaction to normal function. Suggestive evidence of hyperfunction of the adrenal cortex during congestive failure has been obtained.[19,24,25,26]

However, the cellular uptake of considerable sodium by our patients during recovery from congestive failure was inconsistent with regression from adrenal cortical hyperactivity to normal function. Nevertheless, further studies of adrenal cortical function in congestive failure and during recovery are indicated.

Interrelationships of Water and Electrolyte Metabolism During Development of Congestive Failure.—This study furnishes no direct evidence pertaining to water and electrolyte balance during the development of congestive failure. It seems reasonable to infer that movements of water and electrolytes during the development of congestive failure were opposite in direction to those found during recovery. In that event, the extracellular compartment expanded by the retention of water containing sodium in physiological or hypertonic proportions, potassium in isotonic concentrations, and chloride in physiological or hypotonic proportions, whereas the intracellular compartment increased in volume, but lost significant quantities of sodium, potassium, and probably nitrogen.

The shifts of water and electrolyte between the two compartments were probably not secondary to changes in extracellular acid-base equilibrium, since sodium and potassium moved in parallel rather than in opposite directions. Miller[21] has suggested that cardiac edema represents a primary water retention and that shift of sodium and potassium out of the cells is an osmotic compensation for dilution of extracellular cation. However, the demonstration of elevated plasma sodium concentrations during failure in four of our seven patients is inconsistent with this hypothesis. The cellular uptake of water could not be attributed to mechanical forces associated with altered tissue tension from interstitial edema since there was no correlation between the degree of expansion of extracellular and intracellular compartments.

The findings in this study are in accord with the hypothesis that congestive failure is accompanied by an alteration of cellular metabolism, manifested by liberation of ionized base from osmotically inactive constitutents of the protoplasm. Such a change would tend to make intracellular fluid hypertonic in respect to interstitial fluid and would account for the cellular uptake of water and release of sodium and potassium that is apparently associated with the development of congestive failure.

SUMMARY

The clinical and metabolic effects of a diet furnishing 50 mg. of sodium, 1.32 Gm. of chloride, 4.33 Gm. of potassium and adequate water, protein, and total calories were determined in seven patients with severe congestive failure. The major lesion was rheumatic mitral stenosis in four patients and hypertensive and/or arteriosclerotic heart disease in the other three patients.

Prior to the institution of the special diet, the congestive failure had proved refractory to a standard regimen consisting of bed rest, low-sodium diet, digitalization, and frequent mercurial diuretics, carried out for a nine to forty-nine-day control period of hospitalization in four patients and for several weeks under medical supervision at home in two patients. Progressive decompensation developed in the remaining patient despite digitalization at home. The cardiac

failure was manifested by marked passive congestion and edema of both circuits in four patients, and by marked pulmonary congestion but little or no peripheral edema in three patients.

The extracellular volume decreased by an average of 8.28 L. in the four patients with marked peripheral edema and by 1.44 L. in the three with little or no clinically detectable edema. Chloride and water were lost from the extracellular space in isotonic proportions in the two patients with initially normal plasma levels, whereas relatively less chloride was lost in the five patients with initial hypochloremia, permitting a rise in plasma level. Plasma sodium concentrations were initially elevated in four patients and normal in three and maintained a plateau during recovery from congestive failure, indicating parallelism in losses of extracellular sodium and water, even in the presence of hypernatremia. Plasma potassium concentrations were initially normal in all patients and were also maintained at a plateau through proportionate reduction of total extracellular potassium and water.

In six patients there was a net cellular gain of 3.7 to 33.9 Gm. of nitrogen available for protein synthesis, and in one patient there was a loss of 21.6 Gm., attributable to a marked proteinuria.

During recovery from congestive failure on the special diet, the intracellular compartment lost from 230 to 2,890 ml. of water (average 1,325 ml.), but it gained from 115 to 385 meq. of sodium (average 234 meq.) in six of the seven patients and gained significant amounts of potassium in all patients. The cellular uptake of potassium for purposes other than protein synthesis ranged from 62 to 454 meq. (average 259.9) in the four patients with marked peripheral edema and from 97 to 338 meq. (average 222.2) in the three patients with marked pulmonary congestion but little or no peripheral edema. The positive intracellular balances of potassium and sodium observed during recovery probably represented replenishment of a deficit incurred during the development of congestive failure.

The findings in this study are in accord with the hypothesis that the development of congestive failure is accompanied by an alteration of cellular metabolism, manifested by liberation of ionized base from osmotically inactive constituents of the protoplasm, followed by shifts of potassium and sodium out of the cells and water in the opposite direction to maintain osmotic equilibrium with the extracellular compartment. Recovery from congestive failure is accompanied by cellular release of water and uptake of potassium and sodium, with coincident osmotic inactivation of cell base.

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PRESYSTOLIC PULSATIONS OF THE LIVER IN THE ABSENCE OF TRICUSPID DISEASE

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IT IS the purpose of this paper to stimulate interest in the study of the liver and venous pulse tracings and to draw attention to the presence of presystolic liver pulsations in conditions other than disease of the tricuspid valve. Examination of the liver for the detection of pulsations is omitted by most clinicians, particularly when the venous pulsations in the neck appear insignificant. This may account for the lack of an adequate description of the liver pulse curve in the literature and for the paucity of reported cases of tricuspid valve disease.

Systolic liver pulsation is usually diagnostic of tricuspid insufficiency, either organic or functional. In the presence of tricuspid insufficiency, the large size of the liver does not necessarily reflect a severe degree of myocardial insufficiency, since the hemodynamic effects of the tricuspid insufficiency alone, through increased back pressure during systole, favor hepatic enlargement. In rare instances of nodal rhythm, the atrial contraction following or simultaneous with the ventricular contraction may produce a systolic liver pulsation in the absence of tricuspid disease.[1] In these circumstances the full force of atrial contraction can only be expended backward into the venae cavae, since the tricuspid valve remains closed during ventricular systole. A similar mechanism may be found intermittently during certain cycles in complete heart block and ventricular tachycardia when atrial and ventricular contraction occur simultaneously.

Theoretically, tricuspid stenosis would be expected to produce presystolic liver pulsations. However, since most patients with advanced tricuspid valve disease develop atrial fibrillation, tricuspid stenosis generally does not produce characteristic pulsatory signs. Even when normal sinus rhythm is maintained, it is difficult to identify the presystolic liver pulsations by palpation. The heaving systolic pulsations produced by tricuspid insufficiency, which invariably accompanies the stenosis, often mask the presystolic pulsation of much lower amplitude (Fig. 1). Only rarely will the palpating hand perceive the latter as a separate distinct pulsation. Liver pulse tracings in such cases may be of great diagnostic help.

Mackenzie[2] believed that atrial or presystolic liver pulsations are diagnostic of tricuspid stenosis. This concept has prevailed to the present day. Most

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standard texts on cardiovascular disease make brief mention of presystolic liver pulsation only in conjunction with tricuspid stenosis. Dressler's text[3] is a noteworthy exception: "While the presystolic regurgitation wave of the venous pulse was originally thought to indicate tricuspid stenosis, experience has since shown that the same pulsating phenomenon is observed with grave congestion in the right side of the heart, which offers an obstacle to auricular emptying. However, it may be safely said that in the presence of mitral stenosis, a presystolic liver pulsation points with great likelihood to a complicating tricuspid stenosis."

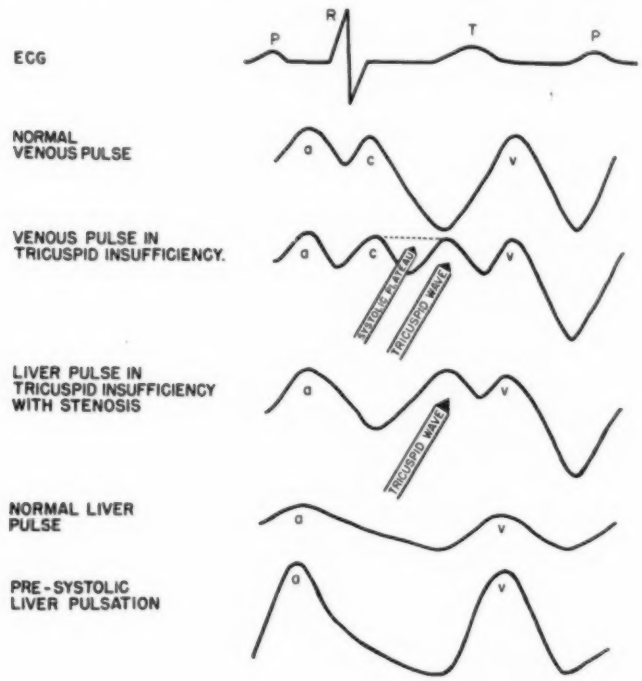

Fig. 1.—Schematic drawings of normal and abnormal venous and liver pulse curves. In tricuspid insufficiency the regurgitating blood and the retrograde pulse wave may cause either a continued systolic plateau (dotted line) or a positive wave in late systole in the jugular pulse curve. Only a late systolic wave will be seen in the liver pulse tracing. Increased amplitude of the normal "a" wave is the cause of clinically perceived presystolic liver pulsation.

In our experience, the latter statement has proved to be fairly accurate. A study of the hearts of patients with chronic rheumatic valvular disease, associated during life with presystolic liver pulsations, has regularly revealed the presence of organic tricuspid stenosis. The only published exception is Turnbull's case[4] of atrial liver pulsation in which aortic and mitral valve disease was found post mortem in the absence of tricuspid valve involvement. In the absence of known rheumatic valvular disease, one should refrain from the diagnosis of tricuspid stenosis merely on the basis of presystolic liver pulsation. Reported instances of presystolic liver pulsation in the absence of rheumatic valvular disease have been rare. Volhard[5] and Wenckebach[6] each observed an atrial liver

pulsation due to pericardial effusion and adherent pericardium, respectively, without any valvular defect. Dressler and Roessler[7] many years later added a third observation of presystolic liver pulsation in a case of Lutembacher's syndrome with severe congestive heart failure.

We have recently observed and studied fourteen patients with presystolic liver pulsation associated with cardiac lesions other than tricuspid stenosis. Although we have observed numerous patients with tricuspid stenosis presenting presystolic liver pulsation, they have not been included in this report. We regard the publication and description of the fourteen cases without tricuspid stenosis as being not only of academic interest but also of clinical value, in view of the diagnostic and prognostic importance of this clinical sign. To be acquainted fully with the instrumental factors will reward the clinician and prevent erroneous diagnostic considerations.

MATERIAL

The fourteen patients included in this report were chosen because a presystolic pulsation was visible or palpable over the liver area and confirmed by liver pulse tracings. Observations and graphic tracings were made also of the pulsation in the cervical veins. The hepatic and venous pulses were each recorded simultaneously with the phonocardiogram and electrocardiogram on a tribeam recorder. The degree of heart failure was noted in each case, and the degree of enlargement of the right cardiac chambers was determined from the teleroentgenogram and fluoroscopy. In several of the patients the latter were determined more accurately by angiocardiography. The pulsations of the right atrium and ventricle were recorded in several patients by electrokymography.

The fourteen patients were divided into three groups. Group I comprised eight cases of congenital heart disease: Lutembacher's syndrome or interatrial septal defect (four cases), isolated pulmonic stenosis (one case), Eisenmenger's complex (one case), and tetralogy of Fallot (two cases). Group II comprised three cases of myocarditis with congestive heart failure: acute bacterial endocarditis, eosinophilic myocarditis, and lupus erythematosus. Group III, a miscellaneous group of three cases, included cor pulmonale with heart failure, congenital aneurysm of the aortic sinus with perforation into the right atrium, and chronic auricular flutter without organic heart disease. The pertinent clinical data of each case are tabulated in Table I.

ANALYSIS OF CLINICAL FINDINGS

Table I shows that marked enlargement of the chambers of the right heart was almost a universal finding. This was true particularly of the patients with congenital heart disease. The sole exceptions were the patient with lupus erythematosus, which was associated with pericardial effusion, and the patient with atrial flutter in whom the heart appeared entirely normal in size and configuration (Fig. 2). Heart failure, although common, was not a constant finding. In the congenital group a significant degree of failure was observed in only two of the eight patients. In the other two groups with acquired cardiac lesions, however, heart failure was more common and more severe, occurring in five of the six pa-

TABLE I. SIGNIFICANT DATA IN FOURTEEN PATIENTS WITH PRESYSTOLIC LIVER PULSATION IN THE ABSENCE OF TRICUSPID STENOSIS

CASE	AGE	DIAGNOSIS	X-RAY EXAMINATION	HEART FAILURE	LIVER SIZE AND PULSATION	JUGULAR VEINS AND PULSE
			I. Congenital Heart Disease			
1. M. N.	22	Lutembacher syndrome	Enlarged to right and left Prominent pulmonary artery Enlarged right atrium (angiocardiogram)	None	Not enlarged Presystolic pulsation	Not distended Presystolic pulsation
2. A. D.	45	Lutembacher syndrome	Marked enlargement to right and left Prominent pulmonary artery	Mild	Slightly enlarged Presystolic pulsation	Not distended No prominent pulsation
3. J. F.	14	Interatrial septal defect	Marked enlargement to right and left Prominent pulmonary artery	Severe	Markedly enlarged Presystolic pulsation	Greatly distended Presystolic pulsation
4. R. C.	28	Interatrial septal defect	Huge globular enlargement Marked right atrial enlargement (left anterior oblique)	None	Not enlarged Presystolic pulsation	Not distended Presystolic pulsation
5. S. G.	16	Isolated pulmonic stenosis	Globular enlargement Pulmonic stenosis (angiocardiogram)	None	Not enlarged Presystolic pulsation	Not distended No prominent pulsation
6. E. C.	24	Eisenmenger's complex	Enlargement to right and left Pulmonary artery dilated Enlarged right atrium (angiocardiogram)	None	Not enlarged Presystolic pulsation	Slightly prominent Presystolic pulsation
7. B. C.	33	Tetralogy of Fallot	"Coeur en sabot" Right ventricular enlargement Right atrial enlargement (left anterior oblique)	Moderate	Slightly enlarged Presystolic pulsation	Distended No prominent pulsation No prominent pulsation

8. H. S.	12	Tetralogy of Fallot Right-sided aortic arch Collateral bronchial artery anastomoses Subacute bacterial endocarditis	Right ventricular enlargement Right-sided aortic arch	None	Not enlarged Presystolic pulsation	Not distended Presystolic pulsation
		II. Febrile Illness; Congestive Heart Failure				
9. B. B.	48	Acute bacterial endocarditis of aortic valve with ruptured cusp Acute myocarditis	Moderate enlargement High amplitude of right atrial systole (kymogram)	Severe	Enlarged Presystolic and systolic pulsations	Distended No prominent pulsation
10. J. A.	19	Eosinophilic myocarditis	Marked enlargement of all chambers	Severe	Marked enlargement Presystolic pulsation	Distended No prominent pulsation
11. L. B.	24	Lupus erythematosus Pericarditis	Slight enlargement to left Pericardial effusion	Moderate	Moderate enlargement Presystolic pulsation	Distended Presystolic pulsation
		III. Miscellaneous Conditions				
12. G. R.	43	Bronchial asthma Cor pulmonale	Enlargement to left Prominent pulmonary artery	Severe	Marked enlargement Presystolic pulsation	Distended Presystolic pulsation
13. A. T.	47	Congenital aneurysm of right aortic sinus with rupture into right atrium	Marked enlargement to the right and left	Severe	Moderate enlargement Presystolic, late systolic, and early diastolic pulsations	Distended Presystolic, late systolic, and early diastolic pulsations
14. N. G.	54	Chronic atrial flutter	No chamber enlargement	None	Not enlarged Presystolic pulsation	Slightly prominent Flutter waves visible

tients. The degree of liver enlargement corresponded closely to the incidence and degree of heart failure. Significant liver enlargement was detected in only one of the congenital group, and in five of six patients in the heart failure and miscellaneous groups. It is also to be seen that presystolic liver pulsation was not always accompanied by prominent pulsation or distention of the cervical veins (Fig. 3). In the congenital heart disease group, prominent venous pulsations were observed in five of the eight patients (Fig. 4), but venous distention occurred only in the two patients associated with heart failure. In the other two groups of 6 cases, cervical vein distention occurred in the five patients in heart failure, but prominent venous pulsations were observed in only three patients.

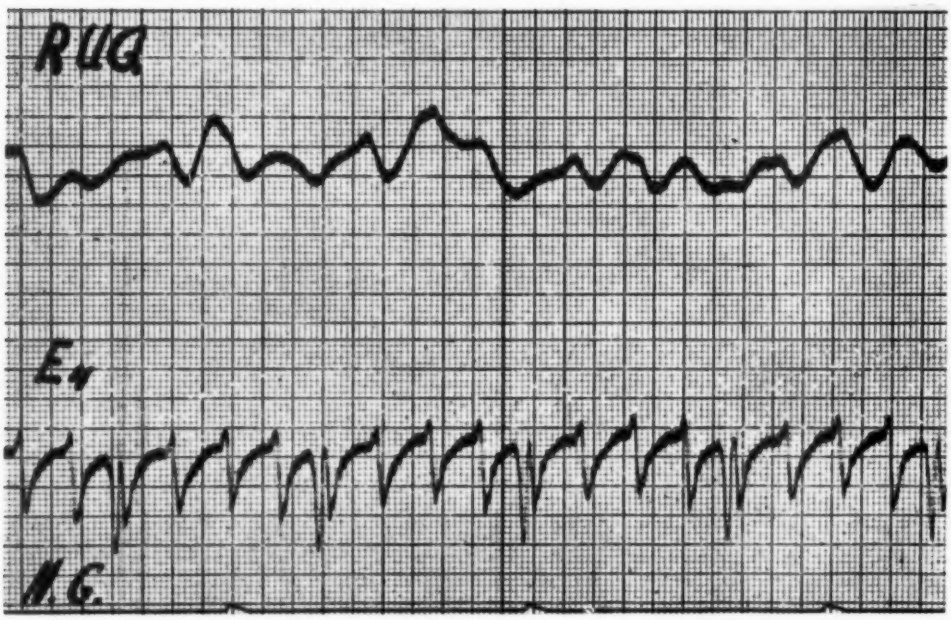

Fig. 2.—Case 14. Chronic atrial flutter of unknown etiology. No cardiac enlargement. Atrial flutter waves are recorded over the right upper quadrant. E_1 represents an esophageal lead recorded at the left atrial level.

ANALYSIS OF LIVER PULSE TRACINGS

In the normal individual, pulsations of the liver are too feeble to be palpated or recorded unless the organ is exposed. When possible to record, the normal tracing consists of an "a" wave, expressing the component hemodynamic events within the right atrium during its systole, and a "v" wave, expressing the events during ventricular diastole. Although the closure of the tricuspid valve is occasionally recorded as a notchlike interruption of the otherwise smooth downstroke of the "a" wave, a typical "c" wave, similar to that of the jugular venous pulse, is not recorded over the liver. If such a wave is present in a liver pulse tracing, caution should be exercised in its interpretation, since it is more likely to be transmitted epigastric, aortic, or apical pulsation during ventricular systole.

To exclude such transmitted systolic pulsations, the liver pulse tracing should not be recorded medial to the right midclavicular line. The reason most often given for the absence of the "c" wave in the liver pulse tracing is that the pulse wave produced by the supposed ballooning of the tricuspid valve into the right atrium at the onset of right ventricular systole is too feeble to be recorded over the liver. In our opinion, the impact of the displaced and distended ascending aorta on the superior vena cava during systole is the most plausible explanation for the "c" wave in the jugular pulse.

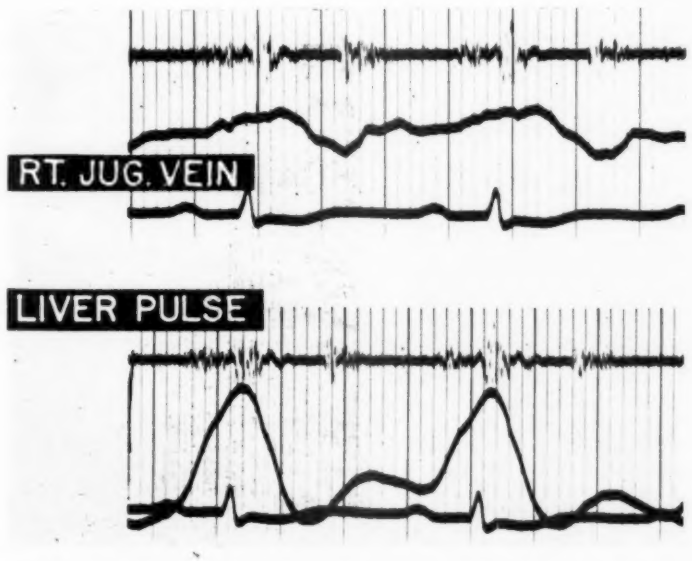

Fig. 3.—Case 2. Lutembacher's syndrome with marked enlargement of right cardiac chambers and pulmonary artery. Presystolic liver pulsations of very high amplitude. Note the contrast with the low amplitude jugular vein pulsations.

During early diastole and sometimes even in late systole, the "v" wave of the liver pulse is recorded similar to that in the venous pulse. The "a" and "v" waves in the liver pulse may follow the respective waves in the phlebogram by 0.02 to 0.04 second. A similar delay may be observed in the late systolic regurgitation wave caused by organic or functional tricuspid insufficiency.

In presystolic liver pulsation in the absence of tricuspid disease, the amplitude of the normally present "a" and "v" waves is markedly increased. This makes the liver pulsations easily detectable by palpation and inspection. A late systolic rising wave which is characteristic of tricuspid insufficiency is invariably absent.

ANALYSIS OF ELECTROKYMOGRAMS

Electrokymograms were obtained in two cases (Cases 6 and 9). These tracings were of particular value in affording a graphic record of the movements of the right cardiac border. Study of the electrokymographic records of both patients demonstrated a striking increase in amplitude of right auricular contraction.

This is well illustrated in the electrokymogram of the right cardiac border obtained in Case 9 (Fig. 5). Downward movement of the kymographic curve represents inward movement of the cardiac border (contraction), and upward movement represents outward movement of the border (filling). It is seen that there is a prominent downward movement of the curve in presystole due to increased amplitude of auricular contraction. The presystolic downward auricular movement is associated with the P wave of the electrocardiogram and precedes the onset of the QRS and carotid pulse curve. The normal ventricular

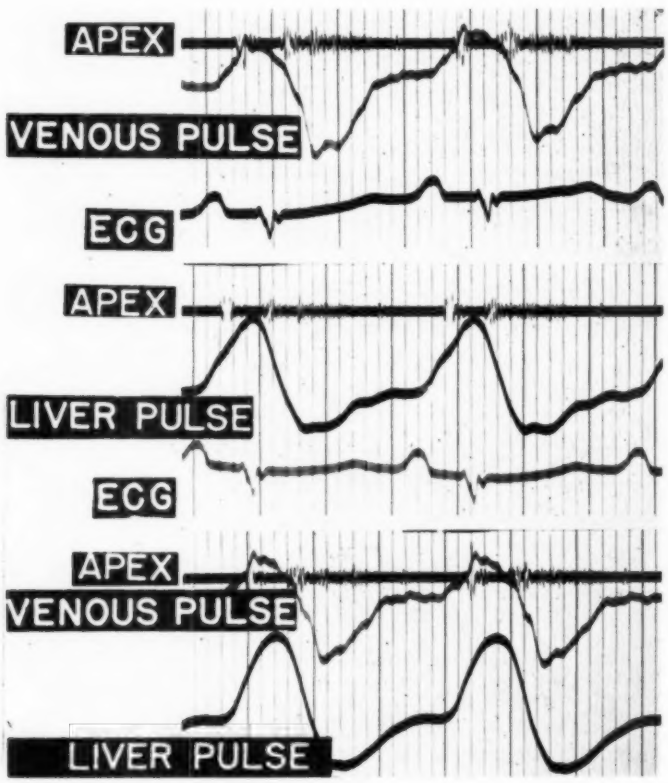

Fig. 4.—Case 4. Interatrial septal defect with considerable enlargement of right atrium. No congestive failure. No venous distension or liver enlargement. The tracings show presystolic pulsations of very high amplitude in the jugular and liver pulse. Note synchronism of venous and hepatic waves. There is a prominent auricular sound in the phonocardiogram.

component of the electrokymogram of the right border is small or absent in this patient, indicating that the movements of the right border are almost entirely auricular in origin. It is evident that the presystolic liver pulsations in this patient were associated with increased amplitude and probably increased force of auricular contraction.

DISCUSSION

Although the causes of hepatic pulsation can be easily understood when functional or anatomical insufficiency of the tricuspid valve exists, the factors producing presystolic pulsation appear more complex. The understanding of this problem is easier if one discards the time-honored concept that liver pulsation is produced by an actual increase in liver volume by regurgitated blood. While this explanation might be entertained in the case of systolic liver pulsation in tricuspid insufficiency, it is untenable in the case of presystolic liver pulsation.

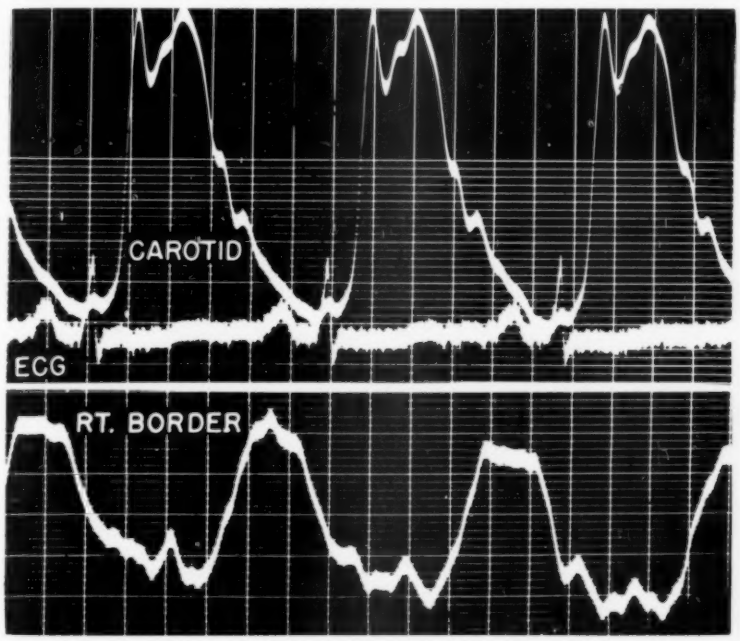

Fig. 5.—Case 9. Acute bacterial endocarditis with ruptured aortic valve, and acute myocarditis and severe heart failure. Electrokymogram of right cardiac border showing a prominent presystolic downward movement due to increased amplitude of right auricular contraction. The right ventricular tug is very small or absent.

It is unlikely that 10 to 20 c.c. of blood from the right atrium would increase the liver size sufficiently to make it easily perceptible. We believe that in tricuspid insufficiency the systolic pulsation seen, felt, and recorded in the jugular vein is due to a pulse wave set off by the contraction of the right ventricle, propagated through the insufficient tricuspid valve to the atrium, superior and inferior vena cava, jugular vein, and liver. In asthenic or cachectic individuals, one gains the impression on inspection and palpation that the liver is moving downward rather than expanding through an increase in volume.

In tricuspid stenosis a presystolic pulse wave is propagated to the jugular vein and liver from the right atrium, which is contracting with increased force against the obstruction at the tricuspid valve. It is our belief that in our series of patients in whom tricuspid stenosis was absent the presystolic liver pulsation

was due also to a presystolic pulse wave propagated from the right atrium. The underlying factor in all of these patients appears to be obstruction to right atrial or ventricular outflow due to increased resistance in the right ventricle or pulmonary circuit. The causes for the latter will be discussed.

The right atrium has no valves to prevent backflow into the great veins during its systole. Keith described angular muscular structures at the entrance of the superior and inferior venae cavae into the atrium. These contract during atrial systole and probably hamper backflow into the large veins. It is unlikely, however, that this damlike mechanism is always adequate, particularly under pathological conditions. It is probable that some reflux occurs normally and under certain conditions, when venous return to the heart becomes greatly increased, it may act as a safety mechanism to prevent right ventricular overfilling from an abundant atrial ejection.

Our interest in this peculiar mechanism was first aroused by our experiences in angiocardiography.[8] In a considerable number of cases, particularly in children, asthenic individuals, and patients with mediastinal tumors and certain congenital cardiac defects, a reflux of the Diodrast-blood mixture into the inferior vena cava, hepatic, and innominate veins was observed. This was assumed to be due to the sudden overloading of the right atrium during the very rapid intravenous injection of 25 to 50 c.c. of Diodrast. However, venous pulse tracings made during the very rapid intravenous injection of 100 c.c. of saline (2 seconds) showed no evidence of systolic atrial filling (tricuspid regurgitation) and only a suggestive increase in all wave amplitudes. Angiocardiographic motion pictures proved that reflux occurred only during atrial systole.[5] It appeared to us, then, that the right atrium and the large veins leading to it acted as a transitional unit, sparing the right atrium and preventing its overdistention by allowing storage of blood in its tributaries. This compensatory mechanism may be called upon when the right atrium has to contract against an increased resistance. This might be brought about by tricuspid stenosis, pericarditis, or pericardial effusion which restrict right ventricular diastole, compression of the pulmonary artery or right ventricle by a mediastinal tumor, cor pulmonale, and certain congenital cardiac defects associated with right ventricular and/or pulmonary hypertension. Increased stroke output of the right atrium as encountered in interatrial septal defect will accentuate these factors.

One would expect that pulse tracings recorded over the jugular vein might be helpful in analyzing these mechanisms. However, they have proved disappointing. A study of cases of tricuspid stenosis with prominent presystolic liver pulsations would often reveal only small "a" waves in the jugular venous pulse tracings and by direct inspection. On the other hand, very prominent "a" waves may be seen at times in normal individuals without concomitant hepatic pulsations. In the present series of patients without tricuspid stenosis, the same discrepancy in the prominence of jugular liver pulsation is found. Only eight patients presented prominent presystolic pulsations in the cervical veins; in the other six patients presystolic liver pulsations were felt and recorded in the absence of increased visible pulsation and prominent "a" waves in the jugular veins.

In our series of patients, the factors possibly responsible for resistance to right atrial outflow and therefore for reflux to the liver were heart failure, right ventricular hypertension (Fig. 6), pericardial effusion, pulmonary hypertension (Fig. 7), and interatrial or aortic-atrial shunts. Congestive heart failure, although a common contributory factor, can hardly be fundamental in the pathogenesis of the presystolic liver pulsation, since a good number of the patients showed no evidence of decompensation. In fact, in the congenital heart disease group, only two patients presented significant degrees of heart failure. In the entire series, severe right heart failure occurred in only five patients, being a particularly prominent feature in Cases 9, 10, and 13. The latter case was complicated by the presence

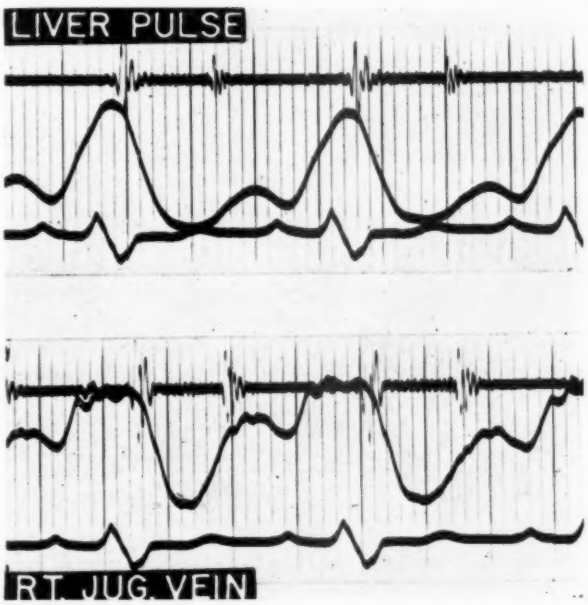

Fig. 6.—Case 5. Isolated pulmonic stenosis. No heart failure, hepatic enlargement, or venous distension. Synchronous presystolic pulsations of very high amplitude are visible in the venous and liver pulse tracings.

of an aortic right atrial fistula. Case 9 was remarkable in that both presystolic and systolic hepatic pulsations were demonstrated by palpation as well as by graphic methods, and at post-mortem examination an intact tricuspid valve was found. The profound right heart failure in this patient was caused by marked dilatation of all cardiac chambers with subsequent insufficiency of the tricupsid valve. At the same time, the right atrial contractions were accentuated by the increased right atrial and ventricular pressure and increased blood volume. All three hemodynamic factors can be directly attributed to congestive heart failure and were responsible for the presystolic liver pulsations in this case.

Acute pericardial effusion was a contributory factor in one patient (Case 11). By increasing intrapericardial pressure, this condition may impede right ventricular filling. The increased resistance to atrial emptying thus created will lead to venous hypertension and increased force of right atrial contraction.

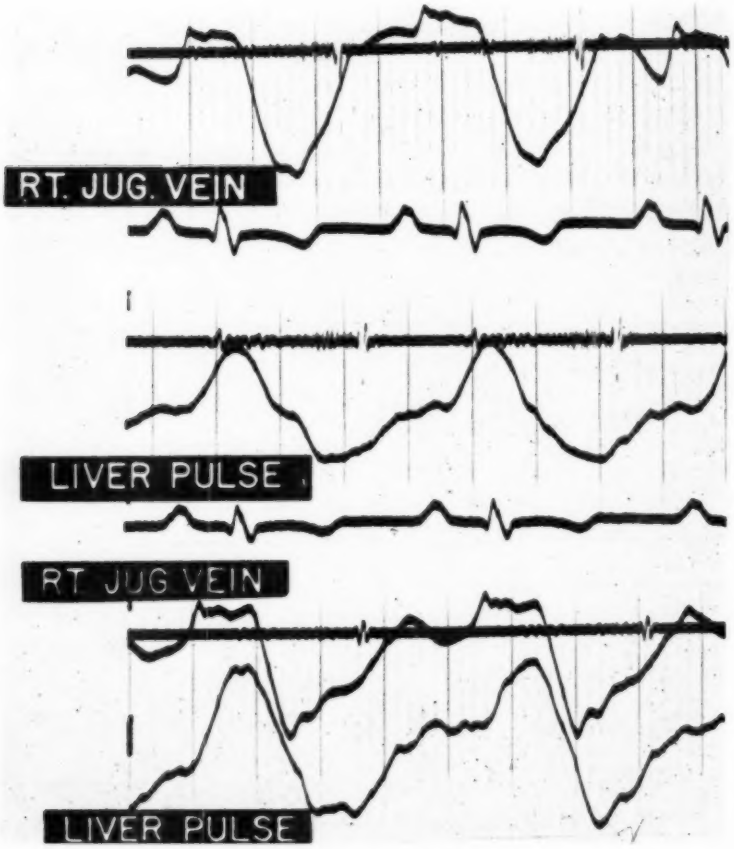

Fig. 7.—Case 6. Eisenmenger's complex. No heart failure or hepatic enlargement. Presystolic pulsations of very high amplitude are present in the jugular and liver pulse tracings. Note that the peak of the "a" wave is reached earlier over the jugular vein than over the liver.

The latter may be manifested by presystolic liver pulsation. In the patient with cor pulmonale with heart failure (Case 12), the resistance to atrial outflow was to be found in the pulmonary arterioles and pulmonary hypertension (Fig. 8).

The group of patients with congenital heart disease was characterized by the uniform presence of enlargement and increased pressure in the chambers of the right heart. In the patient with isolated pulmonic stenosis (Case 5) there was resistance to right cardiac outflow at the pulmonic valve. In the patients with Tetralogy of Fallot (Cases 7 and 8) the increased stroke volume of the right atrium may have acted as an accentuating factor. In the patient with Eisenmenger's complex, the increased force of right atrial contraction seems, at first glance, to have been the sole cause for the presystolic liver pulsation. However, catheterization of the pulmonary artery in this condition has often revealed pulmonary hypertension, which may also increase the resistance to right ventricular and atrial outflow. Whether pulmonary hypertension in Eisenmenger's complex is caused by pulmonary arteriolar constriction due to systemic

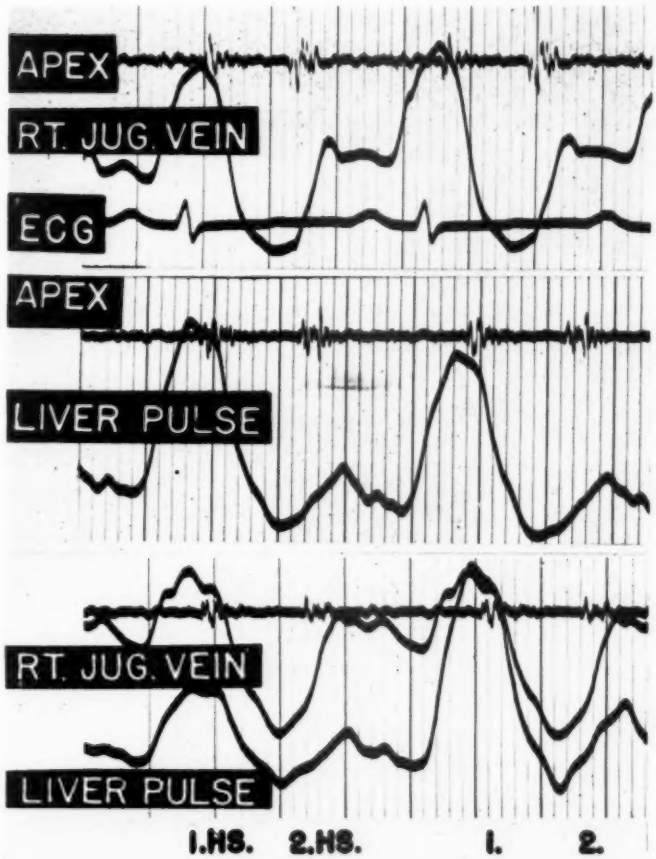

Fig. 8.—Case 12. Cor pulmonale and congestive failure. Synchronous "a" waves of very high amplitude in jugular and liver pulse tracings.

anoxemia or by pulmonary arteriosclerosis due to long-standing increased blood flow is unknown.

Analysis of the patients with interatrial septal defect with or without congenital mitral stenosis (Cases 1, 2, and 3) suggests the presence of an additional contributory, if not predominating, causative factor for the presystolic liver pulsation. During angiocardiographic studies of patients with this lesion, passage of the Diodrast-blood mixture from the right to the left atrium has rarely been observed, even in far advanced cases with congestive heart failure.[8] Moreover, in three patients studied by means of right heart catheterization,[9] the average pressure in the left atrium was found to exceed that in the right atrium by a ratio of 1:2.5 to 1:3. It is conceivable that the left atrial contraction wave can be propagated through the septal defect into the right atrium, particularly to the region of the inferior vena cava. This direction of propagation is favored by the position of the long axis of the atria which is almost vertical (Fig. 9). The vertical axis of the atria, the right atrial hypertrophy, and increased right

atrial stroke volume, as well as the increased right ventricular pressure, constitute the possible causes for the presystolic liver pulsations in this congenital lesion.

In the patient with the aneurysm of the posterior sinus of Valsalva perforating into the right atrium (Case 13), the systolic pulsations were probably caused by the blood flow through the fistula during systole. The presystolic liver pulsations, however, were due to marked overfilling of the right atrium and very advanced congestive heart failure.

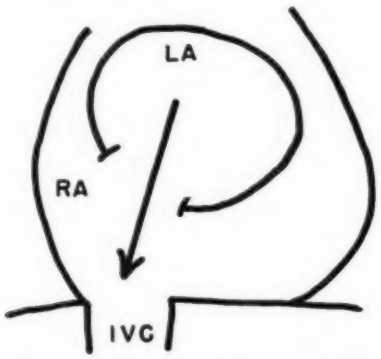

Fig. 9.—Schematic drawing of possible mechanism of presystolic liver pulsation in interatrial septal defect. The arrow indicates the direction of the pulse wave through the interatrial defect.

SUMMARY

Fourteen patients with presystolic liver pulsation in the absence of tricuspid stenosis or organic disease of the tricuspid valve have been described. The underlying hemodynamic mechanism is considered to be resistance to right atrial outflow with reflux to the liver, caused by heart failure, right ventricular hypertension, pericardial effusion, pulmonary hypertension, and interatrial or aortic-atrial shunts.

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ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH PATCHY MYOCARDIAL FIBROSIS IN THE ABSENCE OF CONFLUENT MYOCARDIAL INFARCTION

An Anatomic Correlative Study

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THE electrocardiographic patterns indicative of confluent myocardial infarction have been established and their meaning explained.[1,2] This is also true for the contour and interpretation of the electrocardiograms of transitory coronary insufficiency.[1] However, the electrocardiographic abnormalities consequent to chronic inadequacy of the coronary blood flow in the absence of a remote confluent myocardial infarction are much less clearly defined.[2,3] There is general agreement that myocardial lesions secondary to such a state may produce such electrocardiographic changes as slurring, notching, widening, and decreased voltages of the ventricular complexes, defective auriculoventricular and intraventricular conduction, and abnormalities of the S-T-T configurations.[1-7] It has been further emphasized that these abnormalities are not directly due to the coronary arterial changes but are produced by the myocardial lesions occurring in the presence of a relative insufficiency of coronary flow.[1] Such electrocardiographic abnormalities may be of importance clinically in indicating coronary disease in the absence of congestive failure, angina pectoris, or myocardial infarction. However, similar anatomic lesions may follow the healing of rheumatic or other more obscure myocardial inflammatory conditions and lead to similar electrocardiographic changes. When chronic coronary insufficiency does not produce confluent myocardial infarction, the resultant ischemia may lead to progressive myocardial fibrosis of a disseminated, but patchy, nature.[1] At necropsy, evidence of coronary insufficiency consists of finding such scattered fibrosis. It is apparent that the subject is of sufficient importance to merit further investigation. In the present study this was done by an anatomic and electrocardiographic correlation in ninety-five autopsied cases.

MATERIAL

Ninety-five cases were selected at random from the necropsy files of the hospital. The criterion for the selection of cases was the presence of patchy

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TABLE I.

CASE NO.	AGE AND SEX	DIAGNOSIS*	NECROPSY FINDINGS				ELECTROCARDIOGRAPHIC FINDINGS						
			HEART WEIGHT (GRAMS)	LEFT VENTRICULAR WALL THICKNESS (MM.)	CORONARY ARTERY SCLEROSIS†	MYOCARDIAL FIBROSIS†	LOW VOLTAGE‡	NON-SPECIFIC S-T-T ABNORMALITY	QRS SLURRING	LEFT VENTRICULAR STRAIN	AURICULAR FIBRILLATION	BUNDLE BRANCH SYSTEM BLOCK	MISCELLANEOUS
1	55 F	HHD	350	14	0	++				+			
2	73 F	ASHD	300	12	++	++	++P	+	+		+		
3	62 M	HHD	300	16	+	++		+					
4	56 F	ASHD	250	15	+++	+++		+					
5	85 M	ASHD	400	13	+++	+++	+	+	+			Right	
6	86 M	ASHD	500	18	+	++				+	+		
7	80 F	HASHD	350	13	+++	+++	++P	+	+		+		
8	70 M	ASHD	350	13	++	++	+						
9	57 M	HASHD	500	17	+++	++				+			
10	70 M	ASHD	350	13	++	++		+			+		
11	60 M	ASHD	275	13	++	++	++	+					
12	45 F	RHD	300	17	+	++	++	+			+		
13	57 F	ASHD	250	15	++	++	+P			+			
14	66 M	ASHD	425	12	+	+++	++P	+	+		+		Fig. 1, *F* and *G*
15	67 M	HASHD	625	20	++	+++	++P		+	+			
16	70 F	ASHD	200	13	++	++				+			Fig. 3, *A*
17	40 M	RHD	450	17	0	++	++P	+	+	+			Fig. 3, *B* and *C*
18	59 M	ASHD	350	14	++	++	+	+			+		
19	76 F	ASHD	325	16	+++	++		+					
20	55 M	ASHD	575	17	+++	++	++P	+	+	+			Fig. 3, *D* and *E*
21	55 F	ASHD	500	17	+++	++	+	+					
22	71 M	ASHD	375	17	+++	++		+					
23	48 F	ASHD	350	15	++	++	++P	+	+				Fig. 1, *B* and *C*
24	76 F	ASHD	525	24	+	++				+			
25	65 M	ASHD, RHD	425	12	+++	+++		+			+		
26	84 M	HASHD	500	19	++	+++				+			
27	68 M	ASHD	225	13	++	++		+					
28	62 M	ASHD	400	15	+++	++				+			
29	57 M	HHD	600	23	+	++	+P			+			
30	47 F	RHD	525	15	+	++	++P					Left	Fig. 2, *A* and *B*

31	76 F	ASHD	325	20	++	++		+					
32	58 M	Leucemia	225	14	+	++	+	+	+				
33	57 F	Brain tumor ASHD	250	18	++	++		+					
34	61 M	ASHD	300	15	++	+++	++P	+					
35	56 M	ASHD	350	13	++	++	++		+			Right	
36	81 M	ASHD	300	16	++	++				+			
37	73 F	ASHD	300	16	++	++	++P	+	+				
38	72 M	ASHD	375	12	++	++	++	+					Electrical alternans
39	65 F	Toxic cirrhosis	200	11	+	++	++	+			+		
40	50 F	ASHD	320	7	++	++	+						
41	43 M	ASHD	445	14	+++	++				+			
42	31 M	Pyelonephritis	300	15	+	++	++	+					
43	73 F	ASHD	375	15	++	+++	+P	+	+				Complete A-V block
44	70 M	ASHD, RHD	500	20	+	+++			+	+			
45	37 M	HHD	575	14	+	++	+P	+					
46	49 F	HASHD	450	19	++	++		+	+	+			Fig. 2, C and *D*
47	66 F	ASHD	350	8	++	++		+					
48	73 F	ASHD	400	12	++	++		+	+				
49	79 M	ASHD	400	20	++	++	+		+	+			
50	21 F	RHD	400	16	0	+++	++	+	+				
51	57 M	ASHD	375	14	+	++		+					
52	25 F	Accidental death	300	12	0	++	+						
53	69 M	ASHD	280	12	+++	++	+	+	+				
54	85 F	ASHD	400	18	++	+++	++	+	+				Fig. 1, *A*
55	27 F	RHD	275	8	++	++		+					
56	60 M	ASHD	520	16	+++	+++				+			
57	43 M	HHD	550	22	0	++				+			
58	70 F	ASHD	250	14	+++	+++	++	+	+				
59	63 F	HASHD	320	20	+++	+++	++					Left	
60	64 F	ASHD	200	15	++	++		+					
61	61 M	ASHD	400	14	++	++							Normal ECG
62	61 M	HHD	400	20	+	++	+	+					
63	38 M	HHD	500	18	+	++	+	+					
64	82 M	ASHD	425	12	++	+++	+	+	+				Fig. 2, *F*
65	50 F	ASHD	320	20	++	+++		+					
66	67 F	Gastric CA ASHD	300	15	+	++		+					
67	56 M	HASHD	375	15	++	++	++P	+					
68	67 M	HHD	425	20	0	++	++	+	+				
69	68 F	ASHD	730	25	++	+++				+			

(*Table continued on next page.*)

TABLE I.—CONT'D

CASE NO.	AGE AND SEX	DIAGNOSIS*	NECROPSY FINDINGS				ELECTROCARDIOGRAPHIC FINDINGS						
			HEART WEIGHT (GRAMS)	LEFT VENTRICULAR WALL THICKNESS (MM.)	CORONARY ARTERY SCLEROSIS†	MYOCARDIAL FIBROSIS†	LOW VOLTAGE‡	NONSPECIFIC S-T-T ABNORMALITY	QRS SLURRING	LEFT VENTRICULAR STRAIN	AURICULAR FIBRILLATION	BUNDLE BRANCH BLOCK	MISCELLANEOUS
70	70 F	ASHD	225	10	+++	++		+					A-V block, complete
71	55 F	ASHD	250	9	++	++		+	+			Right	Fig. 2, *E*
72	82 F	ASHD	350	14	++	+++	+P	+					
73	55 M	ASHD	200	11	++	++		+					
74	48 F	HASHD	225	12	++	++	++P	+	+				
75	84 F	ASHD	400	13	+++	++		+					
76	71 M	ASHD	500	20	++	++				+			
77	78 M	Pyelonephritis	400	16	0	++	++P	+					
78	64 M	ASHD	300	15	++	++	+P	+	+				
79	74 F	ASHD	350	17	+++	++				+			Fig. 1, *D* and *F*
80	64 M	ASHD	300	17	+++	++	++P	+	+				
81	70 F	HASHD	500	18	++	+++	+P		+	+		Right	
82	42 F	HAD	425	18	+	+++		+	+	+			
83	60 M	ASHD	400	14	++	+++		+	+	+			
84	80 F	ASHD	325	14	++	+++	+			+			
85	71 M	HHD	325	18	++	++				+			
86	57 M	ASHD	475	12	+++	+++	++						
87	81 F	ASHD	250	6	++	+++	++	+	+		+		
88	35 M	RHD	1250	14	0	+++	++P	+	+		+		
89	50 F	RHD	526	14	0	+++	+	+			+		
90	69 F	ASHD	475	14	+++	+++		+					
91	40 F	Pyelonephritis	250	11	+	++	+	+			+		
92	77 F	HASHD	300	12	+	++		+				Right	
93	59 M	ASHD, RHD	500	15	+++	++		+				Left	
94	58 M	HASHD	625	25	+++	++							
95	44 F	HASHD	400	18	++	++		+					

*HD = heart disease; H = hypertensive; A = arteriosclerotic; R = rheumatic.
†+ = minimal; ++ = moderate; +++ = marked.
‡+ = borderline normal voltages; ++ = definitely small voltages; P = progressive.

myocardial fibrosis in quantitatively moderate to marked degree as arbitrarily designated in the gross and microscopic autopsy protocols. Only those cases were used where electrocardiograms had been taken. Instances of confluent myocardial infarction were not included. Since the myocardial lesions were the sole criterion for case selection, the myocardial fibrosis was not invariably due to coronary artery disease. In most cases the last electrocardiogram had been obtained within three months prior to death; in many cases serial records were available, having been recorded over a period of years. Since the cases were obtained during a time in which only six leads were being recorded routinely, the tracings consisted of the standard limb leads and CF or V precordial leads from positions 2, 4, and usually 5. The criteria for normality and for low voltages have been previously set forth.[1]

RESULTS

I. Anatomic Data.—The essential clinical, pathological, and electrocardiographic findings are presented in Table I and summarized in Table II. In sixty-seven cases the moderate to marked patchy myocardial fibrosis was of the degree which might be expected with the amount of coronary sclerosis and narrowing found. In the remaining twenty-eight cases the degree of fibrosis appeared to be greater than the coronary disease might warrant. However, in fifteen of the latter hearts, there was considerable cardiac enlargement primarily due to left ventricular hypertrophy, which may account for the excessive fibrosis. Hypertensive and arteriosclerotic heart disease were the commonest etiologic mechanisms in the patients studied. In those instances in which rheumatic heart disease or other infectious processes had also been present, the latter may have contributed to the myocardial fibrosis. In thirteen cases, coronary insufficiency was clearly not related etiologically to the fibrosis observed; the underlying mechanism was obscure in eight of these cases, and in five instances healed rheumatic myocarditis was probably the responsible factor.

II. Electrocardiographic Data.—These abnormalities are shown in Figs. 1, 2, and 3.

While an attempt is made to correlate the electrocardiographic with the anatomic findings, it is obvious that other factors not evident anatomically could have led to some of the changes, at least temporarily. Among such factors are medication employed, infection, and anemia of transient and mild character.

Only one normal electrocardiogram was noted in this series. The various electrocardiographic abnormalities encountered in this study are summarized in Table II. In the eighty-two cases (86.3 per cent) in which the myocardial fibrosis could largely be ascribed to the dynamic effects of chronic coronary insufficiency, borderline normal or abnormally small voltages of the QRS deflections in the left chest leads, limb leads, or both were encountered in thirty-nine records (47.6 per cent) (Fig. 1, *C*, *E*, and *G* and Fig. 2, *E*), of which nineteen demonstrated progressively smaller voltages in serial records (Fig. 1, *B* and *C*, *D* and *E*, and *F* and *G*). Had serial records been available in more cases, the incidence of progressively decreased voltages might have been greater. Nonspecific abnormalities of the S-T-T configuration not indicative of ventricular

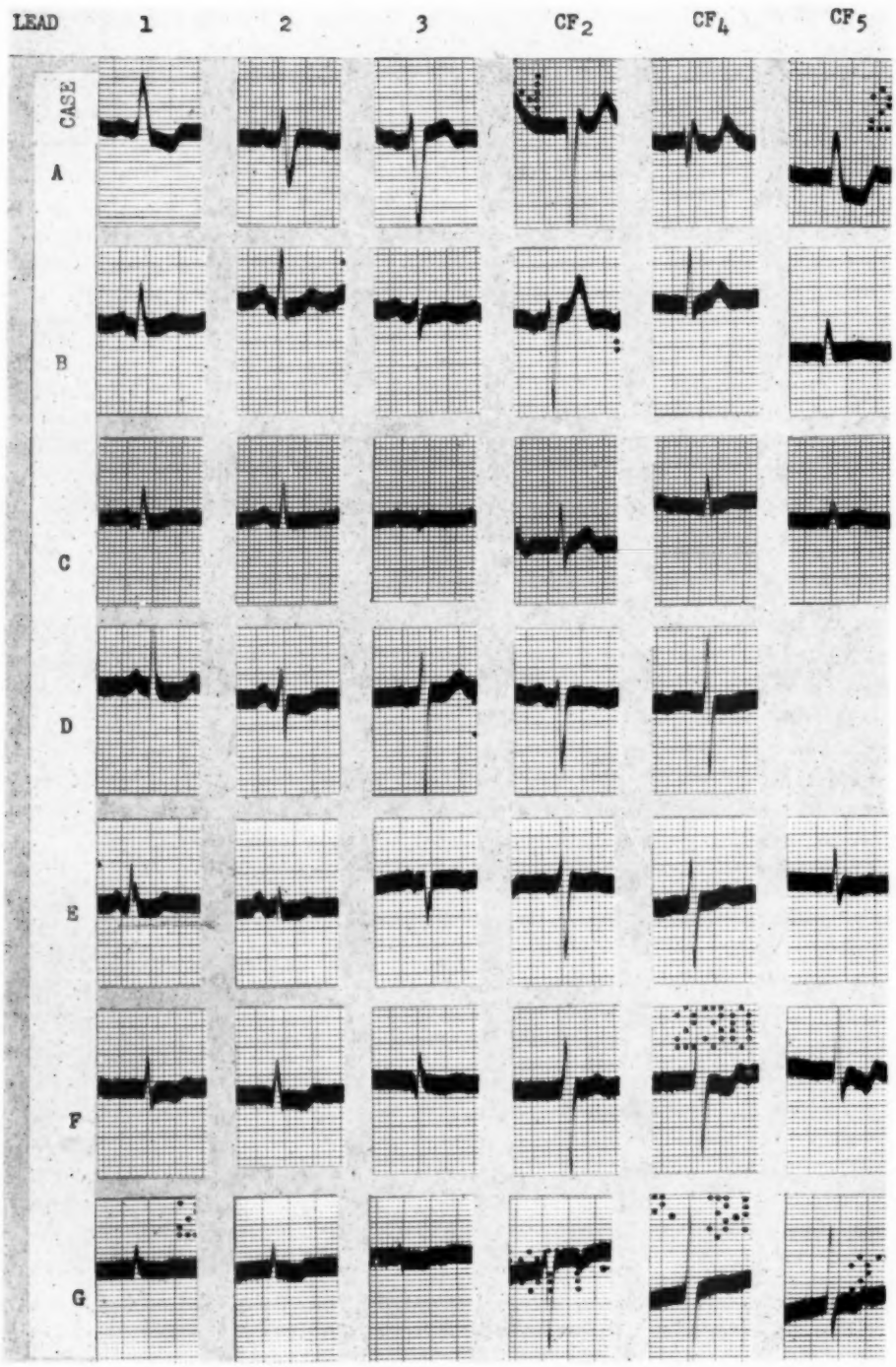

Fig. 1.—*(For legend see opposite page.)*

strain, digitalis contours, or other specific entities were noted in fifty-four records (65.9 per cent) and constituted the greatest single abnormality. These were manifested by an abnormal depression or elevation of the S-T segment and a flattened or inverted T wave. Although not characteristic, some of these changes may have been due to digitalis in patients receiving this medication. In several instances abnormally notched T waves were noted in one or more precordial leads. Marked abnormal slurring and notching of the QRS deflections were observed in twenty-six tracings (31.7 per cent) (Fig. 1, *A*, *C*, *E*, and *F*) and had often become progressively more apparent in serial records (Fig. 1, *B* and *C*, and *D* and *E*).

TABLE II. SUMMARY OF ELECTROCARDIOGRAPHIC DATA IN 95 CASES OF MODERATE TO MARKED PATCHY MYOCARDIAL FIBROSIS WITHOUT PATHOLOGICAL EVIDENCE OF CONFLUENT MYOCARDIAL INFARCTION

ELECTROCARDIOGRAPHIC ABNORMALITY	INCIDENCE OF ELECTROCARDIOGRAPHIC ABNORMALITIES IN 95 CASES OF MYOCARDIAL FIBROSIS		TOTAL
	82 CASES WITH CHRONIC CORONARY INSUFFICIENCY (% OF 82 CASES)	13 CASES WITHOUT CORONARY ARTERY DISEASE (% OF 13 CASES)	
Nonspecific S-T-T abnormality	54(65.9%)	11(84.6%)	65(68.4%)
Small voltages	39(47.6%)	12(92.3%)	51(53.7%)
Borderline normal	19(23.2%)	3(23.1%)	22(23.2%)
Definitely low voltage	20(24.4%)	9(69.2%)	29(30.5%)
Progressively smaller voltages in serial electrocardiographs	19(23.2%)	3(23.1%)	22(23.2%)
Left ventricular strain	23(28.1%)	3(23.1%)	26(27.4%)
Abnormal slurring and notching	26(31.7%)	5(38.5%)	31(32.7%)
Bundle branch block	8(9.8%)	0	8(8.4%)
Small voltages and abnormal QRS slurring and notching	26(31.7%)	0	26(27.4%)
Small voltages and S-T-T abnormalities	31(37.8%)	7(53.8%)	38(40.4%)
Small voltages, abnormal slurring, and abnormal S-T-T changes	17(20.7%)	5(38.5%)	22(23.2%)
Abnormal QRS slurring and S-T-T abnormalities	26(31.7%)	0	26(27.4%)
Auricular fibrillation	8(9.8%)	4(30.8%)	12(12.6%)
Complete A-V block	2(2.4%)	0	2(2.1%)

A left axis shift was usually present. A pattern indicative of left ventricular strain was noted in twenty-three electrocardiograms (28.1 per cent) (Fig. 2, *C*). It was observed in the absence of anatomic hypertrophy of the left ventricle in only one instance (Fig. 3, *A*). At autopsy, the findings were suggestive of brown

Fig. 1.—Record *A*, Case No. 54, shows an instance of slurring throughout the widened QRS complexes, abnormal S-T-T configurations, and deflections of relatively small amplitude in Leads I, CF_4, and CF_5. Record *B*, from another case (No. 23) displays low voltages and slurring in Leads I and CF_5. Record *C* was obtained four months later from the same patient and shows a definite decrease in voltage and other changes. Record *D* from a third case (No. 80) reveals nonspecific S-T-T changes. Three months later, a tracing from the same patient, record *E*, shows marked decrease in voltage and slurring and notching of the QRS complexes. No digitalis had been administered. Records *F* and *G* were obtained from another patient (No. 14) four years apart and again illustrate a progressive decrease in voltage in the limb leads, as well as other changes.

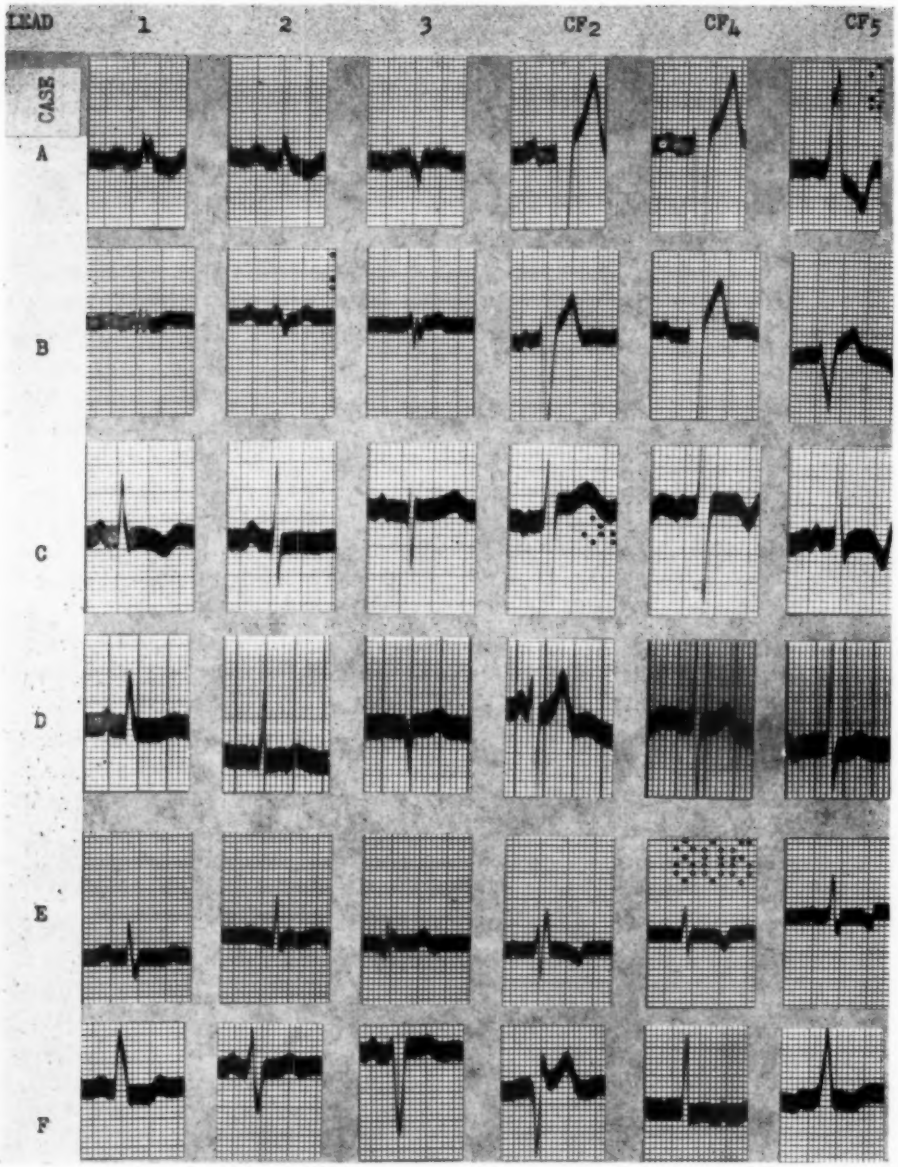

Fig. 2.—Record *A* (No. 30) shows a pattern of left bundle branch system block with widened QRS complexes and small voltage in the limb leads. Four years later, a tracing from the same patient (Record *B*) shows further widening of the QRS interval, smaller voltage in the chest leads (by projecting QRS beyond the record), as well as a reversal of the direction of QRST in CF_5. The transition zone is shifted to the left. These tracings were obtained from a 47-year-old woman with healed rheumatic myocarditis, marked patchy myocardial fibrosis, left and right ventricular hypertrophy, but with only minimal coronary artery sclerosis. Record *C* (No. 46) shows a pattern of left ventricular strain with slurred QRS in Leads I and CF_5. Two months later, an electrocardiogram obtained from the same patient (Record *D*) showed decreased voltage and S-T-T changes which tended to obscure the strain pattern. Record *E* (No. 72) presents a pattern of right bundle branch system block with the complexes of small amplitude. The S-T-T changes in all leads but CF_2 are unexpected in such a pattern. Record *F* (No. 64) shows widened, slurred deflections. Note the deep Q_m CF_2.

atrophy of the heart in this particular case, and the electrocardiographic changes were compatible with those previously described in this condition.[24] In three cases an initial pattern of left ventricular strain disappeared in later records (Fig. 2, *C* and *D*; Fig. 3, *B* and *C*, and *D* and *E*); this was due to a decrease in the amplitude of the QRS deflection, slurring of the ventricular complex, and distorted S-T-T configuration. Patterns of right ventricular strain were not observed.

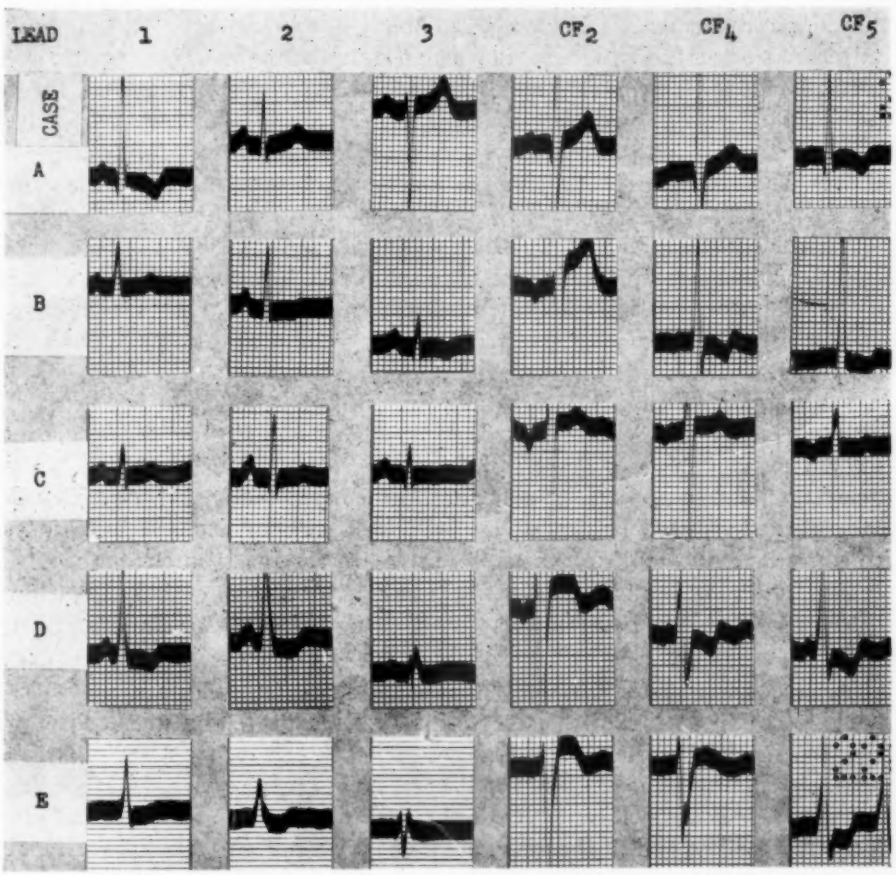

Fig. 3.—Record *A* (Case No. 16) shows a pattern suggestive of left ventricular strain, having been obtained from a patient without anatomic ventricular hypertrophy or known hypertension; the heart at necropsy suggested brown atrophy, and the electrocardiogram was compatible with that previously found in this condition.[24] Records *B* and *C* were obtained five months apart from a 40-year-old man (Case No. 17) with healed rheumatic myocarditis, subacute bacterial endocarditis, and left ventricular hypertrophy. The initial pattern of left ventricular strain is obscured by S-T-T changes and decreased voltages in the second record. Records *D* and *E* were obtained sixteen months apart from a patient (Case No. 20) with moderate myocardial fibrosis, predominantly located in the subendocardial region of the left ventricle. Like the previous case, the pattern in the second record has been altered by decreased voltage and S-T-T changes.

A pattern of complete left or right bundle branch block was encountered in eight cases (9.8 per cent) but was complicated by small voltages in two instances, marked slurring of the QRS deflection in three, bizarre S-T-T configura-

tion in one, and combinations of these in two (Fig. 2, *E*). The latter often became progressively more apparent in those instances where serial records were available.

QRS and/or T-wave contours which resembled electrocardiographic patterns of myocardial infarction were noted in three records (Fig. 2, *F*), despite the absence of confluent myocardial infarction at necropsy.

The abnormalities were often present concomitantly. Small voltages and abnormal slurring were noted in twenty-six cases (31.7 per cent) (Fig. 1, *E*), abnormal slurring and S-T-T changes in twenty-six (31.7 per cent), and small voltages and abnormal S-T-T changes in thirty-one (37.8 per cent). There were seventeen instances (20.7 per cent) in which the combination of slurring and notching, small voltage, and S-T-T abnormalities were noted (Fig. 2, *F*). In these cases there often was widening of the QRS interval. However, the pattern of bundle branch block was not seen in these records. Where serial tracings were available, these changes were often of a progressive nature (Fig. 1, *D* and *E*, and *F* and *G*).

Auricular fibrillation was present in eight cases (9.8 per cent), and complete auriculoventricular heart block was encountered in two records (2.4 per cent).

The frequency of many of the above abnormalities, and particularly the incidence in which these changes were of a progressive nature, might have been greater had serial records been available in more cases.

In the thirteen cases in which the myocardial fibrosis could not be ascribed to the dynamic effects of chronic coronary insufficiency, small voltage was present in twelve instances and was progressive in three cases (Fig. 2, *A* and *B*), abnormal slurring and notching of QRS deflection was found in five, nonspecific S-T-T abnormalities occurred in eleven, and the pattern of a widened QRS interval with slurred small complexes was seen in five cases. Left ventricular strain was noted in three records and auricular fibrillation in four.

DISCUSSSION

When coronary artery disease leads to chronic coronary insufficiency without producing confluent myocardial infarction, the resultant ischemia leads to disseminated focal areas of necrosis and gradual replacement by fibrous tissue in a patchy distribution. Because of the nature of the coronary arterial blood supply and the presence of an intramyocardial pressure gradient,[8] ischemia and fibrosis often occur earliest and to the greatest extent in the subendocardial region of the left ventricle. As the process progresses, these focal areas of scarring may coalesce and at the same time extend to the outer layers of the free wall of the ventricle. Because the net blood flow to the myocardium fails to increase when the ventricles hypertrophy, relative coronary insufficiency may occur earlier in enlarged hearts or with lesser degrees of coronary artery sclerosis and narrowing. The fact that similar alterations were encountered in the presence of myocardial fibrosis secondary to healed rheumatic myocarditis or other lesions and in the absence of coronary artery disease suggests that the electrocardiographic abnormalities are related to the myocardial fibrosis. However, some of the S-T and T-wave changes are doubtless due to the myocardial ischemia itself, especially in those cases where coronary insufficiency was the etiological factor.[1]

In general, the more marked electrocardiographic changes were observed in the cases with more marked myocardial fibrosis. Certain nonspecific abnormalities were frequently encountered as described above. These were present to various extents and in various combinations, occasionally with a QRS interval widened beyond 0.10 second. In those patients in whom serial tracings were available, it was apparent that in many instances the progression of the myocardial damage was associated with progressive electrocardiographic changes. The seriatim changes often consisted of progressively smaller QRS complexes and progressively more apparent slurring and notching of the QRS deflections. There was often a concomitant tendency for slight widening of the QRS interval and for progressively more marked abnormalities of the S-T-T configuration. In many instances, two or more of these abnormalities progressed concomitantly. In twenty-two cases there was concurrent slurring and notching, small voltage, abnormal S-T-T configuration (and often, slight widening of the QRS interval).

Complexes of abnormally small amplitude were encountered particularly in left chest and limb leads. The problem of low voltage QRS complexes has been recently reviewed both in normal persons[9] and in those with intracardiac disease.[10] Frank low voltage can occasionally occur in the absence of myocardial disease when appropriate extracardiac factors are present[1,10] and, even in the absence of such abnormal extracardiac factors, when unusual anatomic and consequent "electrical" positions are present.[1] It therefore does not necessarily reflect intrinsic cardiac disease. However, abnormally small amplitudes occur in hardly more than 1 per cent of tracings obtained from normal persons.[9,10] When it is present in conjunction with other electrocardiographic abnormalities and in both chest and limb leads, the probability of the low voltage being a reflection of intracardiac disease is much greater.[10,20] The duration of the QRS interval can occasionally exceed 0.10 second in normal persons; an interval greater than 0.10 second in association with other abnormalities is less likely to be normal. Marked slurring and notching of the QRS complexes can occur normally in Lead III or near the base line of the deflections in other leads.[1] When it occurs near the apex of a deflection, or in multiple leads, or when associated with gross notching, it is abnormal and almost invariably reflects intrinsic myocardial damage.[3,9,22] This is particularly true in a seres of patients such as this, selected without regard to their electrocardiographic status. The probability of such changes occurring normally in more than a few cases in this study seems remote.[21] In those instances where abnormalities of a progressively more marked nature appeared in serial tracings, there was even less chance of their not being indicative of organic myocardial lesions.[1]

When muscle fibers are replaced by fibrous tissue, local changes in the rate and nature of impulse propagation probably occur during the activation of the ventricles. It has been shown that the subendocardial Purkinje network ramifies throughout most of the free walls of the ventricles and interventricular septum.[11,12] Depending on its location, patchy myocardial fibrosis might interfere with intraventricular conduction distal to the main bundle branches in different parts and in various layers of the free walls of the ventricles. Since both the subendocardial network and the intramyocardial networks freely

anastamose, electrocardiographic evidence of defective conduction in the wall of the ventricle might occur only when sufficiently extensive myocardial lesions had appeared. When myocardial fibrosis is extensive enough it doubtless interferes with the transmission of the activating impulse across the free wall of the ventricle,[6] producing rapid, momentary changes in the direction of the electrical axis and momentary changes in the manifest potential differences between the right and left ventricles.[14,15] Resultant slurring and gross notching of the QRS deflections appear.[3] A slower rate of impulse propagation across the free ventricular wall probably accounts for the widening of the QRS interval. When the activation of different regions of the free wall is delayed beyond the normally late activation of the posterobasal region of the left ventricle,[13] a widened QRS interval might also occur. Rapid momentary changes in the direction of the electrical axis, interrupting the normal spread of the impulse across the free wall in a direction more or less perpendicular to the endocardium, necessarily produce complexes of smaller voltages. Furthermore, the replacement of muscle fibers by scar tissue results in the loss of functioning units normally contributing to the total electromotive forces developed by the heart, and deflections of small amplitude appear.[10] The presence of ischemic areas and regions of fibrous tissue also interferes with repolarization and produces injury currents, both resulting in abnormal S-T segment deviations and abnormal T waves.[1] Furthermore, in such patients polarized and depolarized areas are concomitantly present; these tend to neutralize each other and further effect reduction in electrical potential.[1] When the deeper layers of the left ventricular wall were experimentally damaged, similar changes in the electrocardiograms were produced, lending credence to the theoretical explanation of such abnormalities.[16]

In consideration of the nature of such electrocardiographic changes, it would seem appropriate to designate them as manifesting defective peripheral intraventricular conduction, i.e., peripheral intraventricular block. This problem has been recently studied in this department.[13,17] It was pointed out that the term bundle branch block is too restricted a concept; the expression bundle branch system block was suggested as a term which included defective conduction in the bundle branches as well as in the free walls of the ventricles. It was further pointed out that various electrocardiographic patterns similar to those encountered here could be rationally explained only by assuming peripheral intraventricular conduction defects.

Electrocardiographic patterns of left ventricular strain were encountered with one exception only in patients with anatomic hypertrophy of the left ventricle (Fig. 3, *A*). In the twenty-six instances in which a pattern of left ventricular strain was observed, large voltages such as are often encountered in the limb leads in such tracings were infrequently noted. It is significant that patterns of left ventricular strain were observed in only twenty-six cases, although definite anatomic hypertrophy was present in fifty-nine hearts. The explanation for this discrepancy is partly apparent from the pattern of electrocardiographic change in those cases where serial records were available. In three such instances, early tracings evidenced a pattern of left ventricular strain. During the ensuing years, the early pattern of ventricular strain, apparently associated with the ap-

pearance of progressive myocardial fibrosis, was altered by progressively smaller voltages, slurring of the QRS deflections, and distortion of the typical S-T-T strain configuration until, in time, the pattern of ventricular strain could no longer be clearly recognized. In many of the cases where only the later tracings were available, a pattern of left ventricular strain might have been previously observed.

It was significant that electrocardiographic patterns similar to those encountered in the presence of confluent myocardial infarction were observed in three patients, despite the absence of confluent infarction at necropsy.[1]

A problem which arises is the manner in which abnormalities such as were observed in this study should be designated. This is particularly difficult when similar abnormalities are observed during routine daily interpretation of electrocardiograms when detailed clinical information is not available. The designation ***bundle branch system*** block would seem appropriate in instances where bundle branch block or peripheral conduction defects are clearly seen.[13] In other cases where such definitive patterns are not present, this interpretation cannot be made. Similar electrocardiographic changes occur in the presence of myocardial fibrosis, whether the latter is related to chronic coronary insufficiency, to healed rheumatic myocarditis, or to various other mechanisms, as shown by the thirteen cases in this study in which fibrosis was apparently not caused by coronary artery disease. Since most of the electrocardiographic changes described above are not specifically diagnostic of chronic coronary insufficiency, it would not seem appropriate to make such an interpretation merely from the electrocardiogram, unless evidence of previous confluent infarction could be observed.[18,19] Thus, when similar nonspecific abnormalities are noted during the routine reading of electrocardiograms, it would appear hazardous to say more than that: "Such changes are similar to those known to be associated with myocardial lesions." It should be emphasized that low voltages per se or slight slurring of the QRS deflections must be interpreted with extreme caution, in regard to their being indicative of intrinsic myocardial disease.[2]

However, it is apparent from this study that chronic coronary insufficiency is by far the most common etiological mechanism in the production of significant myocardial fibrosis. When electrocardiographic changes such as were encountered here are found in tracings obtained from patients in older age groups, it is likely that they are due to the myocardial fibrosis occurring in chronic coronary insufficiency.[1,21]

SUMMARY

The electrocardiograms of ninety-five patients were studied whose postmortem examinations revealed the presence of moderate to marked, disseminated, patchy myocardial fibrosis without confluent myocardial infarction. In eighty-two instances the fibrosis was predominantly related to chronic coronary insufficiency. In the remaining cases the underlying mechanism was healed rheumatic myocarditis or was obscure.

In the eighty-two cases where the fibrosis was related to the coronary artery disease, borderline or abnormally small voltages were noted in thirty-nine

instances, nonspecific S-T segment and T-wave abnormalities in fifty-four, left ventricular strain in twenty-three, abnormally slurred and notched QRS complexes in twenty-six, bundle branch block in eight, and patterns simulating those of myocardial infarction in three. These abnormalities were present in varied degrees and variously coexisted in the different tracings.

The electrocardiographic changes were best studied in instances where serial tracings were available. In such cases these electrocardiographic abnormalities, apparently correlated with progressive myocardial fibrosis, frequently became progressively more apparent. In such records, progressive slurring, notching, decreased voltages, abnormal S-T-T configurations, and widened QRS intervals often coexisted.

The mechanism of these changes and their relationship to defective peripheral intraventricular conduction or to concomitant defective bundle branch and peripheral intraventricular conduction has been discussed. Since low voltage, abnormal slurring and notching, and nonspecific S-T-T changes also occurred in the cases where the myocardial fibrosis could not be related to chronic coronary insufficiency, it would appear unwarranted to ascribe routinely such changes to the latter mechanism during the interpretation of electrocardiograms. Nevertheless it is apparent that these electrocardiographic changes, particularly in older persons, are usually caused by the patchy myocardial fibrosis consequent to chronic coronary insufficiency.

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THE INCIDENCE OF RHEUMATIC HEART DISEASE IN NATIVE SCHOOL CHILDREN OF DADE COUNTY, FLORIDA

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THIS report presents the results of a survey performed to determine the incidence of rheumatic heart disease among 1,001 school children born in Dade County, Florida.

Other surveys[1-27] have shown that the incidence of rheumatic heart disease is subject to geographic variation. In milder climates, such as that of southern California[17] and Arizona,[2] the incidence of rheumatic heart disease has been found to be lower than in colder areas such as represented by Connecticut and Wyoming.[2,27]

It has long been the impression that rheumatic heart disease is less frequent and less severe in southern Florida than in more northern areas. The survey presented here represents a systematic investigation, using the experience in precise methodology reported by careful workers who have performed similar studies in other climatic areas.[1,2,5,6,9,12,26]

METHOD

Examinations were performed on 1,001 school children from 10 through 16 years of age, who had been born and reared in southern Florida. These children were selected at random and included 348 white boys, 231 white girls, 198 Negro boys, and 224 Negro girls.

All examiners were members of the attending staff of the National Children's Cardiac Home and included only internists who had a special interest in cardiology.

Each child was initially examined by a minimum of two physicians working independently. Whenever either examiner reported the merest suspicion of organic heart disease, the child in question was subjected to a thorough cardiac work-up at the National Children's Cardiac Home. This included fluoroscopy and teleroentgenograms in the anteroposterior and two anterior oblique views, using barium to detect displacement of the esophagus by an enlarged left auricle. Electrocardiograms, sedimentation rates, and complete blood counts were also performed. Physical examinations were repeated by two other cardiologists of the staff of the National Children's Cardiac Home who had not participated in the original screening of these children. Efforts were then made to integrate

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the findings of all four examiners with the laboratory data. Whenever the findings did not seem to agree, the child was brought back for repeated examinations by multiple observers before a final diagnosis was made.

Murmurs were recorded in terms of location, transmission, timing, intensity, and constancy. Degrees of intensity were graded from 1 to 6, according to the criteria of Levine.[28] Efforts were made to determine variations in murmurs with changes in heart rate, with shifting of the patient from the erect to the recumbent position, as well as with different phases of respiration.

Grade 1 to Grade 2 systolic murmurs, which tended to disappear in deep inspiration and with slowing of the heart rate as the subject relaxed, were usually considered to be functional without further examination. This is in keeping with accepted interpretations of systolic heart murmurs[29,30] and is consistent with the procedure in previous surveys.[18] Whenever any examiner felt that the status of a murmur was the least bit doubtful, however, the child was submitted to the follow-up procedure described above.

RESULTS

The results are tabulated in Table I. Murmurs were heard in 659 children or 65.9 per cent. Evidence of organic heart disease was found in 11 children or 1.1 per cent of the total number of children examined. The murmurs were evaluated as functional in 648 children or 64.8 per cent of the total group, indicating that 98.5 per cent of all the murmurs recorded could not be concluded as being due to organic heart disease.

Among the eleven children in whom evidence of organic heart disease was found, the etiology was diagnosed as rheumatic in five or 0.5 per cent and congenital in six or 0.6 per cent.

In only one of the five children with rheumatic heart disease was there a definite history of rheumatic fever. A history of "growing pains" was elicited in one child, frequent colds and sore throats in two more, and frequent colds in the remaining child. In two of the five cases classified as rheumatic in etiology, there was some indication that the defect might be congenital, but it was felt best to include them in the former group. All five cases of rheumatic heart disease occurred in Negro children in spite of the fact that there were fewer Negroes (42 per cent) than whites (58 per cent) included in this survey.

Congenital heart disease was diagnosed in six cases. Four of these occurred in white children and two in Negroes. Among these were included three cases of interauricular septal defect, two of interventricular septal defect, and one of patent ductus arteriosus.

COMPARISON WITH OTHER SURVEYS

A comparison of the results of various surveys, including the one reported here, is presented in Table II.

The incidence of rheumatic and congenital heart disease in each survey is tabulated according to the method of examination used. Method 1[1] includes surveys where all examining physicians were specially trained in cardiology.

TABLE I. INCIDENCE OF HEART MURMURS IN 1,001 SCHOOL CHILDREN BORN AND REARED IN DADE COUNTY, FLORIDA

	NO MURMUR				FUNCTIONAL MURMUR				RHEUMATIC HEART DISEASE				CONGENITAL HEART DISEASE				TOTALS			
	WHITE		NEGRO		WHITE		NEGRO		WHITE		NEGRO		WHITE		NEGRO		WHITE		NEGRO	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
	139	133	27	43	206	97	167	178	0	0	3	2	3	1	1	1	348	231	198	224
Total white	272				303				0				4				579			
Total Negro			70				345				5				2				422	
Total male		166				373				3				4				546		
Total female		176				275				2				2				455		
Grand total		342				648				5				6				1001		

TABLE II. SUMMARY OF SURVEYS ON RHEUMATIC HEART DISEASE IN CHILDREN OF SCHOOL AGE

LOCATION	REFERENCE	NO. EXAMINED	RHEUMATIC HEART DISEASE		CONGENITAL HEART DISEASE	
			METHOD 1	METHOD 2	METHOD 1	METHOD 2
Denver	Wedum[1]	1051 1845	16.3	4.8	2.7	0
Eureka Redlands	Sampson[17]	2450 2635	20.0 3.8		0.7 0.76	
So. Arizona	Paul and Dixon[2]	1019	5.0			
New Haven	Paul[11b]	1836 — —	25.0 38.5	11.4		
Montana and Wyoming	Paul and Dixon[2]	688	45.0			
Cincinnati	Wilzbach[26]	5623		5.2		2.3
Philadelphia	Cahan[9]	33293		5.0		0.9
Boston	Robey[12]	119337		4.5		0.5
Louisville	Weiss[5]	41905		3.6		1.6
San Francisco	Sampson[25]	13338		2.2		1.4
Cincinnati	Rauh[4]	85389		2.9		1.5
New York City	Halsey[7]	44000		4.3		0.7
Dublin, Ga.	Quinn[18]	401	10.0		5.0	
Bath, England Bristol Gloucestershire, Somerset, Wiltshire and Swindon	Savage[21]	7500 54673 53501 42804 43398		1.28 7.72 1.03 2.17 1.5		
Dade County, Florida	Present paper	1001	5.0		6.0	

Grouped under method 2 are surveys where screening was performed by school physicians and suspects were checked by cardiologists.

Wedum and co-workers[1] have emphasized that any valid attempt to compare the results of surveys in different geographical areas requires a preliminary evaluation of the method of examination used in each. The use of method 1, in which all examinations are performed by trained cardiologists, would be expected to yield a higher percentage of positive findings in any given area than would method 2. Thus Wedum and co-workers,[1] who performed surveys in Denver, found the incidence of rheumatic heart disease to be 16.3 per 1000 by method 1 and 4.8 per 1000 by method 2. A discrepancy of a similar degree was

reported by Paul[1b] in New Haven. Here the incidence of rheumatic heart disease was 38.5 per 1000 by method 1, and 11.4 per 1000 by method 2. In each case, more than three times (3.4) as many cases were found when method 1 was used.

The incidence of 5.0 children with rheumatic heart disease reported in this series of 1,001 school children in Dade County, Florida, using method 1, is similar to the low incidence reported in two other areas of like climate: Redlands, California (3.8 per 1000) and southern Arizona (5.0 per 1000).

This survey revealed a somewhat higher incidence of congenital heart disease (6.0 per 1000) than has been reported in previous surveys of this kind.

SUMMARY

A survey of the incidence of rheumatic heart disease in 1,001 school children born and reared in Dade County, Florida, is described and discussed. The frequency of such disease in these children is shown to be similar to that found in other surveys performed by the same method in areas having a mild subtropical climate and is of a smaller magnitude than that found in more northern localities.

This survey was made possible through the cooperation of the Dade County Board of Public Instruction and the Dade County Health Department. Those who assisted in the examinations were Drs. Herbert Eichert, Sanford Levine, Rose London, David Nathan, Julius Oshlag (deceased), Murray Reckson, Maurice Rich, Reuben Rochkind, Paul Unger, and S. Charles Werblow. Dr. F. Hernandez, senior resident physician, did the lion's share of the laboratory studies.

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A SIMPLY PREPARED, STANDARDIZED, AND RELATIVELY STABLE THROMBOPLASTIN EXTRACT FOR ESTIMATION OF PROTHROMBIN TIME

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THE altered physiology induced by Dicumarol is reflected in prolongation of the "prothrombin time." Regardless of the dosage employed, the conduct of the therapy is determined by the extent of the induced hypoprothrombinemia. To establish this, serial estimations of the accelerated clotting time (prothrombin time) must be made. With the exception of very few workers,[1,2] it has been universally accepted that the single-stage method of prothrombin bio-assay (accelerated clotting time) is best suited for following Dicumarol-induced hypoprothrombinemia. Plasma factors other than prothrombin are rendered constant in this procedure with the aid of a standard excess of thromboplastin, so that the coagulation time of the plasma thus accelerated becomes an index of the plasma prothrombin activity. In the procedure a standardized optimum concentration of calcium is added to oxalated plasma. Thromboplastin represents a mixture of organic materials which are obtained from different animal tissues. The activity of the thromboplastin varies according to the source, the methods used in its preparation, and the mode of preservation. When preparations of thromboplastin of different activities are used to estimate the prothrombin time of a given sample of plasma, the results will vary significantly. Because of this, it has been the practice of most workers to establish the prothrombin time of normal plasma simultaneously and to use this as the standard of reference. There are serious objections to this procedure because the clinician is left at the mercy of the normalcy of a single control plasma. To obviate this, it has been found more suitable to use a relatively stable thromboplastin preparation whose normal range of activity is established by examination of a larger series of normal plasmas. It is also important that the thromboplastin have a sensitive range of activity and that subsequent preparations can be made to compare satisfactorily in activity with the selected normals. This permits valid comparison of serial estimations of the prothrombin time made on different days. Thus, the clinician can learn instantly whether the prothrombin time is rising or falling.

For the purpose of estimating prothrombin time, the ideal thromboplastic substance would be one which is a stable, active, single chemical entity. In the

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absence of this ideal, we must choose a more complex thromboplastin preparation which exhibits the desired activity and can be prepared each time to give reproducible results. It should not be too active, since it may then mask the more subtle changes in prothrombin activity, and the clinician would be apt to administer too much Dicumarol. In our experience, rabbit-lung thromboplastin is the best currently available preparation. It gives reproducible results in the optimum range of activity (about 15 seconds for undiluted plasma and 38 seconds for 12.5 per cent plasma).

Thus the most satisfactory thromboplastin may be summarized as one which possesses the following characteristics: (1) optimum sensitivity, (2) relative stability, (3) consistency from vial to vial, and (4) simple preparation.

This paper describes results obtained with a new preparation of thromboplastin, which more nearly approaches the above desirable characteristics than any other preparation available up to the present time.

The material was prepared in a dried form which required only the addition of distilled water. The study consisted of a comparison of the activity of this preparation with that of a well-established standard rabbit-lung thromboplastin. The new preparation "Simplastin"* is a dried extract of thromboplastin with the reagents calcium chloride and sodium chloride included.

PROCEDURE

Studies were made to determine the activity and stability of the experimental thromboplastin extract. The preparation was compared with a standardized rabbit-lung thromboplastin whose activity was known to be within the range found to be optimum by the authors. All estimations of the prothrombin time were made by the Link-Shapiro modification of the Quick one-stage technique.[4] Estimation of the prothrombin time of whole and diluted (12.5 per cent) plasma was made in each instance.

1. Comparison was made using normal plasma. The data are recorded in Table I. The activity of each of the preparations was practically identical in each case.

TABLE I. COMPARISON OF PROTHROMBIN TIME AS ESTIMATED USING THE STANDARD AND THE EXPERIMENTAL THROMBOPLASTIN PREPARATIONS

PREPARATION	NO. PATIENTS	PROTHROMBIN TIME (SECONDS)					
		WHOLE PLASMA RANGE	MEAN	S.D.*	12.5% PLASMA RANGE	MEAN	S.D.
49479†	50	12–17.5	14.6	±1.1	33–44.6	38.7	±2.5
T83‡	20	14.2–18.0	15.6	±0.9	36.8–44.0	39.4	±1.8

*S.D. = Standard deviation.
†Desiccated rabbit lung of standardized optimum activity.
‡Experimental dried thromboplastin extract ("Simplastin").

*The new thromboplastin, "Simplastin," was originally prepared by two of the authors, R. L. K. and E. J. W., of the Chilcott-Maltine Laboratories. A fraction containing the thromboplastin activity of lung and brain tissue was dried under high vacuum. The dried extract was stored in capped vials at 5° C. At the time of use, the addition of 4.0 ml. distilled water provides a reconstituted extract containing sodium chloride and calcium in concentration suitable for the Link-Shapiro method.

2. Comparison was made using hypoprothrombinemic plasma induced by Dicumarol. The results are recorded in Table II. In this study also the results obtained with both preparations of thromboplastin were practically identical.

TABLE II. PROTHROMBIN TIME OF PLASMA AFTER DICUMAROL AS DETERMINED WITH STANDARD AND EXPERIMENTAL THROMBOPLASTIN PREPARATIONS

PATIENT	PROTHROMBIN TIME (SECONDS)			
	49167*		T83†	
	100%‡	12.5%	100%	12.5%
H. S. B.	17.5 23.0 38.5	36.9 55.0 115.0	17.0 24.4 40.0	38.0 57.8 121.0
B. M. I.	17.1 23.0 21.1	48.1 68.0 62.2	18.0 23.6 21.7	43.0 64.0 68.0
I. L. L.	15.7 22.1 34.0	35.0 53.0 109.0	20.0§ 22.6 32.6	46.0§ 58.0 101.0
S. S. B.	20.6 27.5 33.0	55.2 63.1 96.0	22.0 25.0 31.0	55.7 61.9 93.0

*Desiccated rabbit lung of standardized optimum activity.
†Experimental dried thromboplastin extract ("Simplastin").
‡Concentration of plasma.
§Plasma possibly contaminated when these tests were made.

3. The effect of storage at various temperatures upon the activity of the experimental preparation was studied. Table III records the results. It was found that storage at 5° C. for periods varying between 20 and 31 days did not significantly alter the activity of the thromboplastin preparation. Storage at temperatures varying between 20 and 28° C. for 29 days was followed by no change in activity. Similar findings were obtained after storage at 37° C. for 10 days and following this at 5° C. and again at 37° C. for one day each. Storage at 49° C. for 10 days, 5° C. for one day, and 49° C. for one day produced no change in activity of the preparation. However, storage at 100° C. for 80 minutes altered the activity of the preparation significantly, and after four hours at 100° C. the activity became strikingly reduced.

DISCUSSION

The purpose of anticoagulant therapy is to achieve a state of hypocoagulability of the blood adequate for antithrombotic effect without inducing bleeding.

Because of the numerous variables occurring from patient to patient, such as differences in extent and duration of the pathologic processes, inconstancy in the pre-existing state of coagulability of the blood, and potential alterations in the integrity of the vascular walls, it has not been possible to establish in terms of fixed or absolute values the extent of inhibition of clotting which would be in every case predictably effective therapeutically and free of the hazard of bleeding.

TABLE III. EFFECT OF STORAGE AT VARIOUS TEMPERATURES ON ACTIVITY OF EXPERIMENTAL THROMBOPLASTIN ("SIMPLASTIN") IN DESICCATED FORM

TEMPERATURE °C.	NO. DAYS STORED	PLASMA PROTHROMBIN TIME (SECONDS)	
		WHOLE	12.5%
5	20	16.0	40.5
	27	16.0	41.5
	28	15.1	41.2
	31	15.9	41.1
Room 20-28	29	15.9	39.9
*37, 5, 37	10, 1, 1	16.1	40.9
49	16	15.2	39.1
†49, 5, 49	10, 1, 1	15.9	40.2
100	80 minutes	19.3	47.1
100	4 hours	23.6	61.4

*37° C. for ten days and at 5° C. and 37° C. for one day each.
†49° C. for ten days and at 5° C. and 49° C. for one day each.
All samples of thromboplastin kept in lyophilized dry form two to eight weeks at 5° C. before being used.

In respect to Dicumarol, clinical experience has demonstrated that prolongation of the prothrombin time of whole plasma to about two to two and one-half times the normal, and of the diluted (12.5 per cent) plasma to about three times the normal is a safe and therapeutically effective range.[3] The best conduct of long-range induced hypoprothrombinemia remains to be established.

The authors advocate a method of intermittent dosage which has appeared to be clinically more suitable than the more commonly used "maintenance" dose method. A full discussion of this has been described in another publication.[4] Briefly stated, the advantage of the intermittent dose method is that it avoids excessive accumulation of Dicumarol in the body. After the initial dose, none is given until serial estimations of the prothrombin time demonstrate that the Dicumarol in the body is being disposed of. Thus *repeat doses are given only when the prothrombin time is falling, never when it is rising.*

However, regardless of the schema of Dicumarol dosage employed, the therapy demands serial estimation of the prothrombin time by a method which is both reliable and sensitive.

In order to compare reliably the results obtained by serial estimation of the prothrombin time, it is imperative that the thromboplastin used be of constant activity so that a normal range is fixed. The preparation described in this communication is held to possess this quality. It is stable within wide temperature ranges after many days. At 100° C. or higher the thromboplastin undergoes rapid deterioration.

The number of reports appearing in the literature of fatal or near fatal hemorrhage induced by Dicumarol therapy is increasing strikingly.[5,6] One realizes that only a small segment of the total of such accidents is recorded.

Undoubtedly, there are different factors which contribute to this picture, but the common denominator seems to be made up of overdosage and estimation of prothrombin time of questionable reliability. The former has been discussed fully in an earlier publication[1] and will not be dwelt upon at this time. The latter is the chief concern of the present paper. In most of the reports it is apparent that the techniques employed for estimation of prothrombin time leave much to be desired. Many clinicians continue to report results in percentage values, despite the fact that this has been shown to be either meaningless or misleading, unless the characteristics of the thromboplastin used are known. The clinician should decide which level of hypoprothrombinemia in units of prothrombin time he wishes to achieve on the basis of the activity of the thromboplastin which he employs. With this knowledge, and providing he continues to use thromboplastin of constant activity, he can plot a curve of the results of serial estimations of prothrombin time and thus determine readily if the prothrombin time is rising or declining. He can then decide whether or not further administration of Dicumarol is needed. Because of its constancy in activity, the thromboplastin extract herein described should prove most helpful in the conduct of Dicumarol therapy.

The clinician who has hesitated to employ Dicumarol therapy because of the difficulty encountered in laboratory control should now be able to conduct this therapy with considerable assurance and safety.

In addition, the new preparation offers the advantage of economy in time of preparation and greater accuracy because of less manipulation in making the extract. The operator need only add a stated quantity of distilled water and the material becomes ready for use. Extracting, centrifugation, or filtering are entirely eliminated, thus avoiding some sources of error.

SUMMARY

A standardized preparation of thromboplastin which becomes ready for use after the addition of only distilled water and which is reliable and of optimum sensitivity is described. It is believed that this should add considerably to the safety of Dicumarol therapy, so that the goal of adequate therapeutic effect with minimum danger of hemorrhage can be achieved.

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CALCIFICATION OF THE LEFT ATRIUM IN RHEUMATIC HEART DISEASE

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MACCALLUM[1] directed attention to left auricular endocarditis as a frequent pathological change in rheumatic heart disease. The lesions, which now bear his name, were described in all stages from the early acute to the healed, scarred, thickened patch. However, calcification is uncommon, and extensive calcification is so unusual that it has been the subject of only isolated pathological case reports.[2,3] The rarity of the clinical appreciation of this entity merits this presentation.

The diagnosis of left atrial calcification has been made in four patients with rheumatic heart disease within the past four years. In one, post-mortem verification has been obtained. These four bring the total number of reported cases of clinically recognized left atrial calcification to nine. Begg[4] in 1945 reported one case, and more recently Epstein[5] described three, one of which also appears in a textbook[6] of roentgenology. Another textbook of roentgenology[7] records an additional case.

CASE REPORTS

CASE 1.—E. F. was a 37-year-old white man with known heart disease since the age of 13 years. There was no history of rheumatic fever. Symptoms of congestive heart failure first appeared at the age of 31 years and from that time on necessitated frequent prolonged periods of hospitalization.

Clinical findings on his last hospital admission were: a chronically ill appearance, cyanosis, râles at both lung bases, auricular fibrillation with a ventricular rate of 72, a markedly enlarged heart with systolic mitral and aortic thrills, double mitral and aortic murmurs, a rough systolic murmur over the tricuspid area, blood pressure 100/68 mm. Hg, a liver 4 fingerbreadths below the right costal margin, marked collateral venous circulation over the abdominal wall, and minimal ankle edema.

The electrocardiogram showed auricular fibrillation and right axis deviation. The roentgenographic findings are described in Fig. 1.

Despite the usual cardiac regime, the congestive heart failure remained intractable. Three months after admission the patient suddenly became disoriented and unresponsive; he remained in this condition until he died forty-eight hours later. The clinical diagnosis was: rheumatic heart disease with mitral, aortic, and tricuspid stenosis and insufficiency; cardiac cirrhosis of the liver; and terminal cerebral embolus.

At necropsy the heart weighed 700 grams, and there was deformity of the mitral, aortic, and tricuspid valves with stenosis and insufficiency. The left atrium was markedly dilated and hypertrophied and was lined with diffusely thickened, irregular, and wrinkled endocardium.

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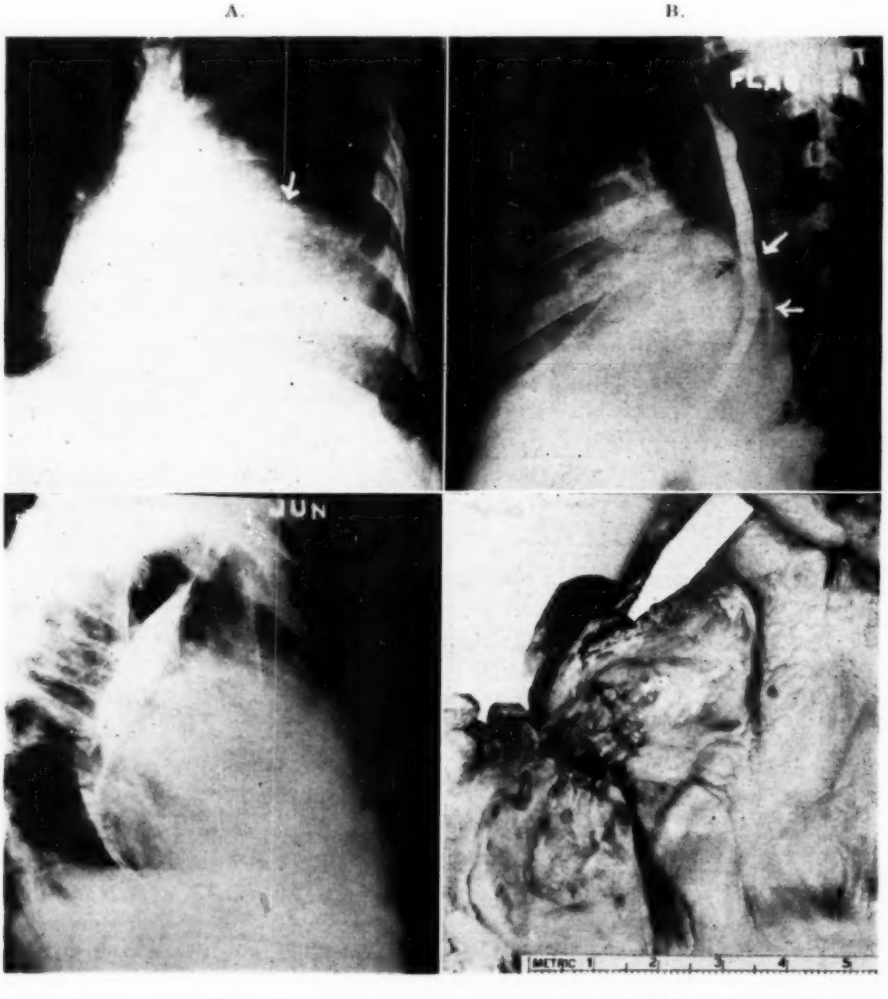


Fig. 1.—Case 1. *A*, Posteroanterior position. A narrow horizontal band of calcification is noted extending medially from the left cardiac border in the region of the left auricle.

B, Left anterior oblique position. A double-lined area of calcification is noted in the left auricle just below the elevated left main bronchus. This extends inferiorly within the posterior margin of the cardiac shadow.

C, Right anterior oblique position. The barium-filled esophagus is displaced posteriorly by the enlarged left atrium. A few small linear areas of increased density, presumably within the left atrial wall, can be identified in the original roentgenogram.

D, Post-mortem specimen of the same heart looking into the left auricle. Above and below the point of the arrow are the areas of calcification of the left auricle, which is represented by the double line of calcification seen in Fig. 1, *B*.

Calcified plaques were found in the posterior wall and near the fossa ovalis. The left auricle was completely calcified in its peripheral portion. The adjacent areas of the atrium were similarly involved (Fig. 1). The mitral orifice was slitlike, and calcified deposits were noted within the valve leaflets. There was no other valvular, endocardial, pericardial, or myocardial calcificaton

Microscopic sections of the left atrium showed slight thickening of the epicardium, hypertrophy and fibrosis of the myocardium, marked hypertrophy of the subendocardial smooth muscle, and irregular thickening of the endocardium with subendothelial calcium deposits.

CASE 2.—I. F., a 48-year-old white woman, has had eight admissions to this hospital between 1934 and 1948. There was no past history of rheumatic fever. For the year prior to the first hospital admission, there had been progressive increase in fatigue and dyspnea. Six months before this admission, there had been a six-week episode of polyarthritis and fever, followed by persistent dyspnea and palpitation.

On examination the findings were those of rheumatic heart disease with an enlarged heart, mitral stenosis and insufficiency, aortic insufficiency, auricular fibrillation, and congestive heart failure. The electrocardiogram showed auricular fibrillation and no axis deviation. Roentgenography of the heart indicated marked horizontal and vertical enlargement of the left atrium, moderate enlargement of the right atrium, and a marked prominence of the pulmonary artery segment.

On the second hospital admission three and one-half years later for congestive heart failure, the clinical findings and the electrocardiogram were essentially the same. Roentgenography of the heart now revealed elongation of the left ventricle, moderate enlargement of both inflow and outflow portions of the right ventricle, and enlargement of both atria as previously described. On admission two and one-half years later for congestive failure, hypertension (blood pressure 162/110 mm. Hg) was also noted.

Subsequent admissions over the ensuing years were for severe congestive heart failure. The clinical findings were not significantly altered except for the development of an aortic systolic murmur not present in earlier years. On the sixth admission in May, 1947, calcification of the left atrium was first detected (Fig. 2).

CASE 3.—L. L., a 52-year-old white woman, had been followed at this hospital from 1932 to 1949. There was a history of chorea at the age of 12 years and acute rheumatic fever with polyarthritis and fever when she was 20 years old. The first symptoms of decreased cardiac reserve appeared at the age of 25 years, but hospitalization for congestive heart failure did not occur until she was 34 years old.

On the first admission in 1932, she was found to have an enlarged heart with mitral stenosis and insufficiency, aortic insufficiency, auricular fibrillation, and congestive failure. Roentgenographic examination showed considerable rounding and elongation of the left ventricle, straightening of the left upper cardiac border, and elevation of the left main bronchus by upward enlargement of the left atrium. The following year there was, in addition to marked enlargement of the outflow tract and moderate enlargement of the inflow tract of the right ventricle, moderate enlargement of the right auricle, and marked horizontal enlargement of the left atrium, which now formed part of the right upper cardiac border.

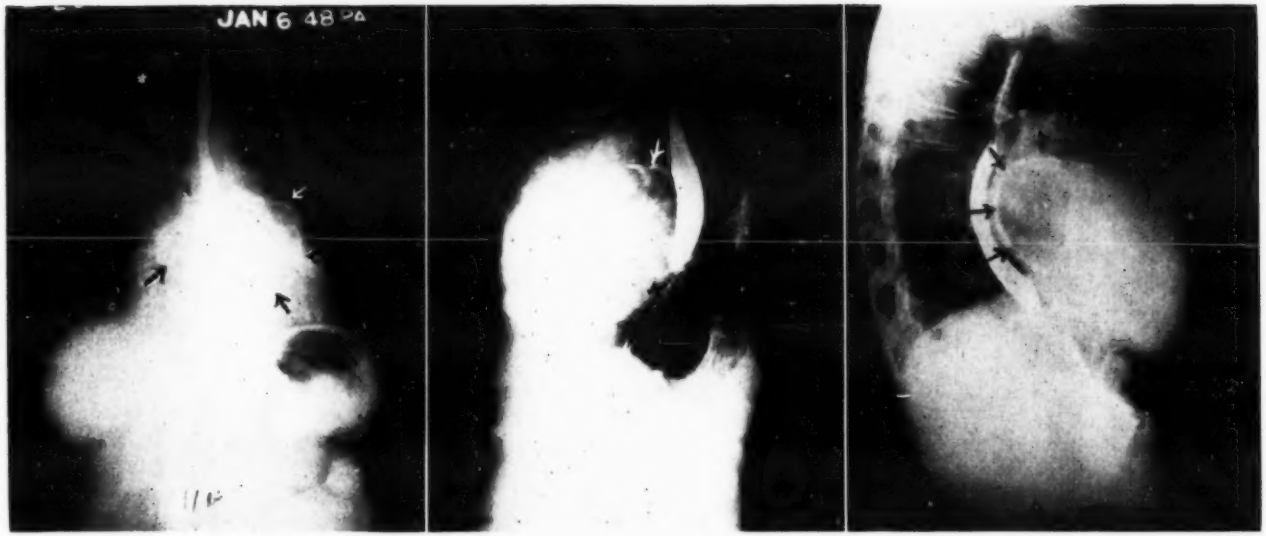
On the third admission for congestive failure in 1939, there were no significant changes in the clinical or roentgenographic findings. On the fourth admission in 1941, there was an increased prominence in the pulmonary artery-conus region, dilatation of the secondary (hilar) branches of the pulmonary arteries, and further enlargement of the left atrium posteriorly. At this time it was also noted that the murmur of aortic insufficiency was no longer audible, and it was not heard thereafter.

After this hospitalization she was followed in the Outpatient Department. In 1946, complete paralysis of the left vocal cord, presumably due to the enlarged left auricle, resulted in permanent hoarseness. In May, 1949, she was hospitalized at a state mental institution where she died shortly after. Autopsy permission was not obtained.

Although numerous roentgenographic studies of the heart had been obtained on this patient over a seventeen-year period, atrial calcification first became demonstrable in December, 1948 (Fig. 3).

CASE 4.—A. B., a 48-year-old woman, was admitted to the hospital in January, 1947, because of symptoms of congestive heart failure. There was no history of rheumatic fever. Palpitation, dyspnea, and orthopnea had been present for ten years prior to admission.

Physical findings on admission were: a markedly enlarged heart, a systolic apical thrill, harsh systolic and diastolic apical murmurs, an aortic systolic murmur, auricular fibrillation with a



A. B. C.

Fig. 2.—Case 2. *A*, Posteroanterior position. A complete ring of calcium is seen outlining the entire periphery of the left atrium. The left auricle forms a part of the left border lying between the pulmonary artery contour and that of the left ventricle. The barium-filled esophagus is deviated to the right.

B, Left anterior oblique position. The upper and lower margins of the left auricle are clearly outlined by a calcific ring, the posterior margin being obscured by the barium-filled esophagus. Fairly marked enlargement of both atria and of the inflow portion of the right ventricle also is indicated. The left ventricle does not appear to be enlarged.

C, Right anterior oblique position. Almost the entire left atrium is ringed with calcium. Enlargement of this chamber has displaced the barium-filled esophagus posteriorly. There is marked prominence of the pulmonary artery-conus segment.

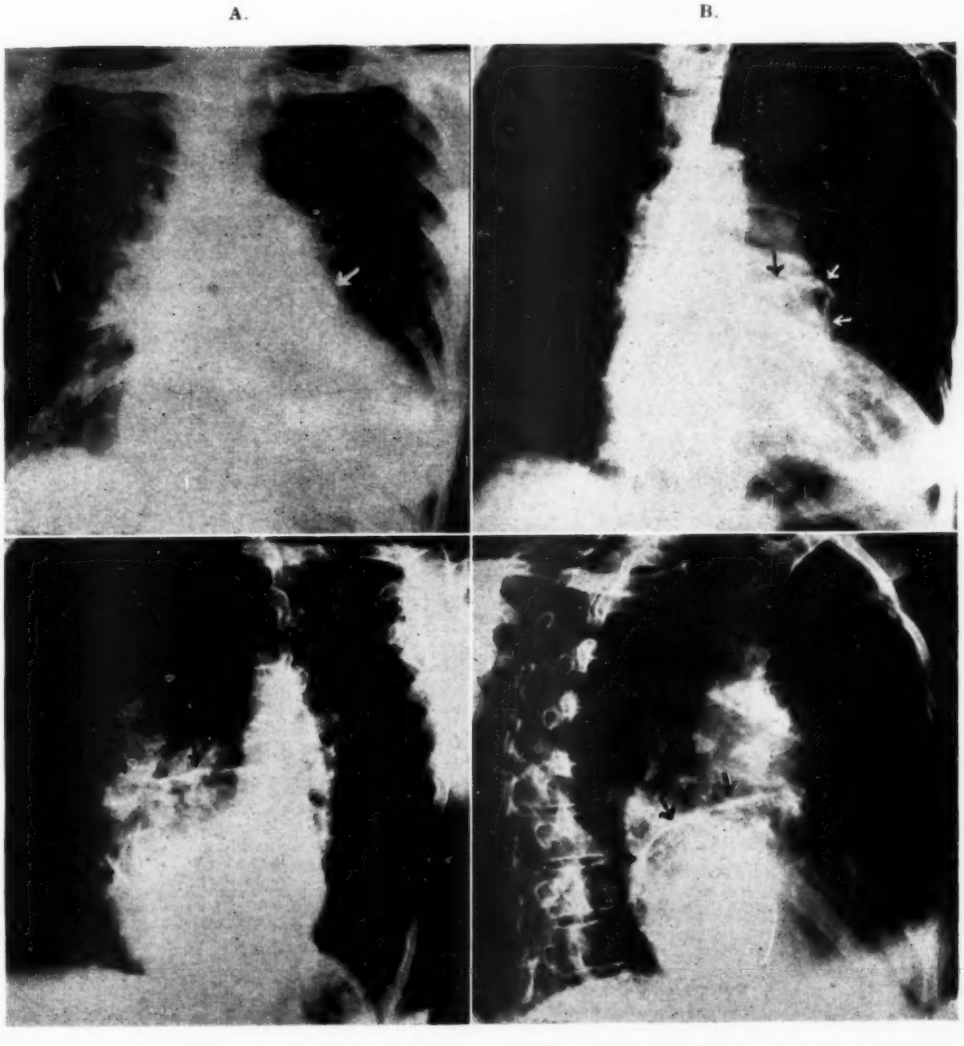


Fig. 3.—Case 3. *A*, Posteroanterior position. A small area of calcification may be noted within the left border of the heart between the prominent pulmonary artery and the left ventricle.

B, An overexposed view with the patient very slightly in the right anterior oblique position clearly outlines the left atrium in all but its right margin.

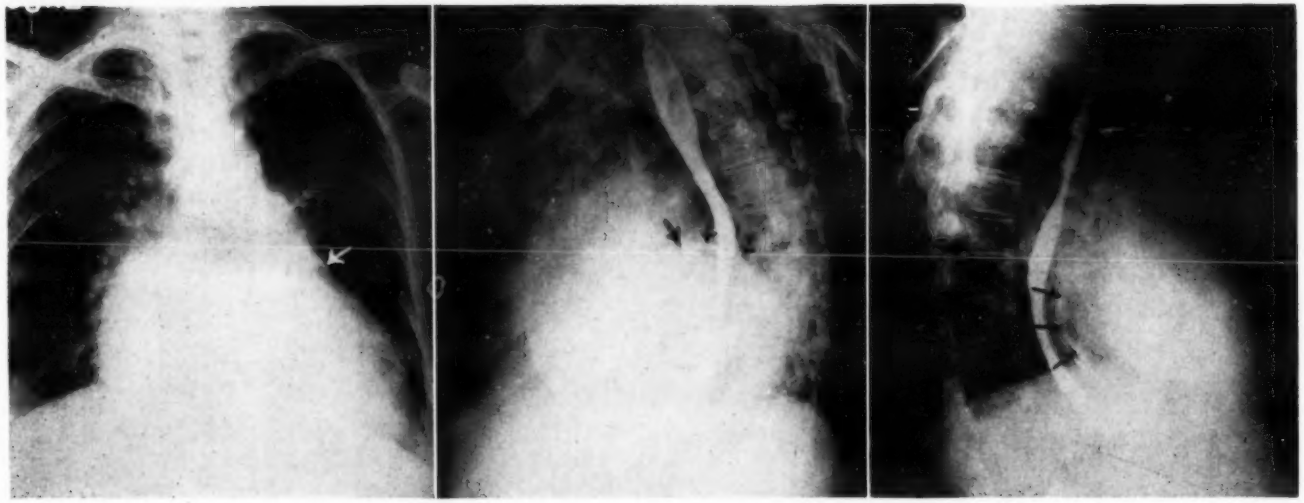
C, Left anterior oblique position. Calcification of the superior and anterior margins of the left atrium are clearly seen.

D, An overexposed view in the right anterior oblique position clearly outlines the calcified superior border and much of the posterior border of the enlarged left atrium.

ventricular rate of 88, signs of fluid at the right base, a liver enlarged to 4 fingerbreadths below the right costal margin, sacral and ankle edema, and a blood pressure of 210/130 mm. Hg.

The electrocardiogram showed auricular fibrillation with marked right axis deviation. The roentgenographic findings are demonstrated in Fig. 4.

The manifestations of failure responded well to routine cardiac therapy, and she was discharged improved one month after admission. The clinical diagnosis was: rheumatic and hypertensive heart disease with enlarged heart, mitral stenosis and insufficiency, and auricular fibrillation.



A. B. C.

Fig. 4.—Case 4. *A*, Posteroanterior position. A narrow line of increased density representing calcification of the left auricle is noted along the left cardiac border between the prominent pulmonary artery and the left ventricle. The left atrium probably extends to the right cardiac border. The left ventricle is markedly enlarged.

B, Left anterior oblique position. A horizontal, crescentic segment of calcified left atrium crosses the barium-filled esophagus, extending to either side of it. Fairly marked left ventricular enlargement is seen. The other chambers are not too clearly delineated but appear enlarged.

C, Right anterior oblique position. A heavy margin of calcification is noted in the region of the posterior wall of the left atrium. The calcification extends upward and anteriorly along the left auricular margin but is less clearly outlined. The barium-filled esophagus is displaced posteriorly by the left atrial enlargement, and anteriorly there is bulging of the pulmonary artery-conus segment into the retrosternal space.

She was readmitted with congestive heart failure in April, 1948. The physical findings were the same as on the previous admission, and the roentgenographic findings were unchanged. She was discharged improved after one month. In October, 1949, she was again hospitalized for heart failure and died two weeks later in acute pulmonary edema. The clinical and roentgenographic findings were similar to those previously described. Permission for autopsy was not obtained.

DISCUSSION

Clinically these patients with atrial calcification do not differ from the usual cases of advanced rheumatic heart disease with predominant mitral stenosis. The subjective manifestations, objective findings, and natural history of the disease follow a fairly common pattern. There is nothing other than the roentgenographic findings to suggest the presence of this type of atrial involvement. The presence of recurrent laryngeal nerve involvement in Case 3 may not be attributed to the calcified left atrium, for it has been described in mitral stenosis with dilatation of the left atrium without calcification.

Probably a small number of cases are not detected due to technical difficulties in the obtaining of complete cardiac roentgenograms. For purposes of contrast and to obtain greater cardiac detail, our technique has been one of slight overexposure of the cardiac shadow. Despite this, however, only four cases have been observed over a four-year period during which time approximately 250 patients with long-standing rheumatic heart disease have been so examined.

The location and extent of the calcification leaves little doubt that it represents endocardial calcification of the left atrium, even in the nonautopsied cases. The right anterior oblique view especially shows the general contour of the dilated left atrium with its posterior deviation of the barium-filled esophagus. In the left anterior oblique position the relation of this chamber to the elevated left main bronchus is clearly seen. Except for one case (No. 2) in which the entire chamber is outlined in all positions, the posteroanterior view fails to show the auricular calcification to maximum advantage; here calcification of the left auricle itself can be recognized.

It is interesting that in three of the four patients the left auricle (appendage) forms a distinct portion of the left border of the heart between the left ventricular segment below and the pulmonary artery segment above. Identification of this segment has been subject to controversy. This was denied by Epstein who stated that only infrequently will the dilated left atrium form a border on the left side of the cardiac silhouette. Electrokymographic studies[8] show that even in the normal heart auricular pulsations are obtainable at the junction of the left ventricular and pulmonary artery segments in the posteroanterior position.

Differentiation of left atrial calcification from other forms of cardiac calcification should offer little difficulty. The calcification within the wall of a ventricular aneurysm or of a thrombus within the aneurysm is recognizable by the appearance of the bulge and the location of the calcification. The thin linear streaks representing calcification of coronary arteries are recognizable by their location and lack the thickness and density of atrial calcification. Aortic and mitral valvular calcifications have a more central location in all views of the cardiac silhouette, are rarely extensive, and roentgenoscopically should be recog-

nizable by their characteristic motion. Pericardial calcification, if located only posteriorly and inferiorly as seen in the right anterior oblique position, could offer difficulty in proper interpretation. However, pericardial calcification is often more extensive and usually may be demonstrable at sites incompatible with the location of the left atrium.

It is conceivable that auricular endocardial calcification might be combined with pericardial calcification to form a diffuse picture, or that the presence of calcified mitral and aortic valves might be responsible for dense shadows in addition to those outlining the left atrium, thus making identification of each difficult. In general, however, the following appear to be significant features:

1. The identification of predominant left atrial and right ventricular enlargement in a patient with mitral valvular deformity of long standing.
2. The presence of calcifications in the area of the left atrium, especially in the right anterior oblique position anterior to the displaced barium-filled esophagus, and in the left anterior oblique view where upward enlargement of the left atrium approaches, displaces, or compresses the left main bronchus.
3. The absence of calcified areas elsewhere within the heart shadow that might then suggest a more diffuse distribution of calcareous deposition with just a fortuitous concentration in the region of the left atrium.

SUMMARY

Four cases of rheumatic heart disease with calcification of the left atrium are described. Criteria for recognition of left atrial calcification are presented.

ADDENDUM

Since the submission of this paper for publication, eight additional cases of auricular calcification in rheumatic heart disease have been reported (Miller, G., Becker, I. M., and Taylor, H. K., Auricular Calcification, AM. HEART J. **40**:293, 1950).

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MERCUMATILIN (CUMERTILIN): A NEW MERCURIAL DIURETIC FOR THE TREATMENT OF CONGESTIVE HEART FAILURE

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ON THE basis of the pharmacologic data reported by Blumberg and associates[1] and the clinical data of Shapiro and Weiner[2] on a new coumarin-mercurial diuretic, mercumatilin (Cumertilin),* it appeared desirable to include this preparation in our general study of mercurial diuretics. Although the value and use of mercurial diuretics for the treatment of advanced congestive heart failure have been thoroughly established, there remains the necessity for controlled evaluation of the various preparations useful for this purpose. Studies on other mercurial diuretics[3] have been reported previously from our laboratory.

The chemical structure of mercumatilin, 8-(2′-methoxy-3′-hydroxy mercuri-propyl)-coumarin-3-carboxylic acid-theophylline, is depicted in Fig. 1. It differs from the currently available mercurial diuretics in that the usual mercuriated allylamide grouping is replaced by an allyl group attached directly to the ring carbon atom of the heterocyclic ring structure. It is a theophylline salt with each cubic centimeter of mercumatilin containing approximately 132 mg. of the compound, of which 93 mg. is mercumallylic acid equivalent to approximately 39 mg. of mercury. The theophylline content is approximately 50 mg. per cubic centimeter of which 11 mg. is excess theophylline. The solution of the sodium salt is adjusted to a pH of approximately 7.3 and appears to be stable.

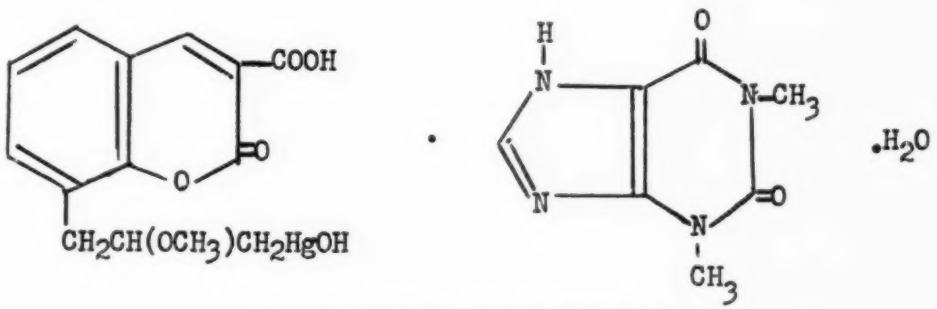

Fig. 1.—Structural formula of mercumatilin.

From the Cardiac Section of the Medical Service, Bronx Veterans Hospital.

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*The authors are indebted to Endo Products, Inc. for the supply of the diuretic and other aid in connection with this investigation.

METHOD

The diuretic effectiveness and safety of the new mercurial was determined in comparison with meralluride (Mercuhydrin). The latter diuretic was chosen since it is the one commonly used for intramuscular administration. The study followed the pattern of previous investigations[2] and was concerned with the determinations of the following data for both diuretics in comparable groups of patients: (1) the predictability of obtaining a satisfactory diuresis, i.e., weight loss of 3 pounds or more of edema fluid over a period of 48 hours when 2 c.c. of the preparations were administered intramuscularly, (2) the degree of diuresis, (3) the local tolerance and degree of irritation at the site of intramuscular injection, and (4) evidence of systemic toxicity including idiosyncrasy and kidney irritation.

A total of twenty-eight patients with the usual organic heart diseases and varying degrees of congestive heart failure comprised this investigation. Twenty patients received mercumatilin for 44 trials, and fourteen patients received meralluride for 41 trials. Five patients were observed for both diuretics. All patients were in chronic congestive heart failure, and most had been observed for periods of weeks or months before they were included in the investigation. Since all patients were bedridden, they had already achieved the maximum effects of complete physical rest. All patients, although digitalized and receiving the maximum daily tolerated dose of a digitalis preparation as maintenance, continued to have accumulation and persistence of edema. The daily maintenance dose, however, was discontinued in five patients prior to administration of the mercurial diuretic because of adjustment of dosage or the occurrence of digitalis toxicity. The diuretic effectiveness of mercumatilin and meralluride was observed without concomitant administration of ammonium chloride in 21 out of the 44 trials and 14 out of 41 trials, respectively.

In all instances the diuretics were administered intramuscularly in the dosage of 2 c.c. at about the same time in the morning. The patients were weighed daily. Repeated injections of a mercurial were given only if the weight curve had achieved a constant level or indicated an accumulation of edema fluid. Frequent urine examinations were performed during the period of observation. A diuretic response was considered to be effective only if the patient lost at least 3 pounds (1.3 kg.) of edema fluid over a period of 48 hours. In the five patients who received both diuretics, the degree of congestive heart failure was approximately the same at the time the comparison was made.

RESULTS

The effectiveness of mercumatilin as compared to meralluride for the removal of edema fluid from patients with congestive heart failure is presented in Table I. On the basis of predictability of obtaining a satisfactory diuresis, it will be noted that mercumatilin is as effective as meralluride. For mercumatilin the predict-

ability of response was 59.1 per cent of 44 trials in twenty patients, and for meralluride the predictability was 58.5 per cent of 41 trials in fourteen patients.

TABLE I. PREDICTABILITY OF OBTAINING A SATISFACTORY DIURESIS

DIURETIC	ROUTE OF ADMINISTRATION	NO. PATIENTS	TRIALS	DIURESIS					
				SATISFACTORY		INADEQUATE		FAILURE	
				NO.	%	NO.	%	NO.	%
Mercumatilin	Intramuscular	20	44	26	59.1	14	31.8	4	9.1
Meralluride sodium	Intramuscular	14	41	24	58.5	12	29.2	5	12.2

The degree of diuresis for both diuretics was also similar. The weight loss for the trials with meralluride averaged 4.05 pounds, while that for mercumatilin averaged 3.15 pounds. This difference in average weight loss was not considered to be significant since it is within the limits of the experimental method.

It was noted that the omission of ammonium chloride did not materially alter the predictability of response of mercumatilin. This was not true of meralluride. With mercumatilin, the response of patients receiving ammonium chloride was 66.6 per cent, while those patients not receiving ammonium chloride demonstrated a response of 50.0 per cent. In the patients who received meralluride, the predictability of response with and without ammonium chloride was 77.7 per cent and 21.4 per cent, respectively.

In the five patients receiving both mercurial diuretics, mercumatilin was observed for 16 trials with an average weight loss of 4.2 pounds. Meralluride was observed for 20 trials with an average weight loss of 4.1 pounds.

None of the patients receiving mercumatilin presented any appreciable degree of local irritation other than that which would be expected from the insertion of an intramuscular needle and the injection of a bland medication. mercumatilin appeared to be less irritating following intramuscular injections than meralluride. None of the patients presented any induration or nodules with either preparation.

Mercumatilin did not produce any evidence of systemic toxicity. None of the patients evidenced any abnormalities in the urinalysis.

DISCUSSION

Although considerable advances have been made in the development of effective and safe mercurial diuretics, there is a continued necessity for further investigation along these lines. Studies on the predictability of response and degree of diuresis achieved with the mercurial diuretics available to date have been presented in a recent review.[4] To achieve a maximum diuresis and therefore to be assured of a predictable response, it is necessary to adhere very closely to a

regime including digitalization, physical rest, and the use of acidifying salts. It would be desirable to obtain, if possible, a mercurcial diuretic which would minimize or obviate the necessity for all or any of these important factors. It is, therefore, with considerable surprise that we noted that the lack of concomitant administration of ammonium chloride did not materially alter the likelihood of a satisfactory diuresis when mercumatilin was used. This is in contrast to experiences with meralluride and with other mercurial diuretics.[3] Although the number of patients used in this phase of the investigation may not have been sufficiently large, the trend is unmistakable and is in line with similar experiences of others[5] who are at present investigating this diuretic. The ability of a diuretic to produce a satisfactory response in the majority of patients without the use of ammonium chloride would be a decided advantage.

Evidence[4] has been presented by one of us (R. C. B.) which applies to all mercurial diuretics: Any single preparation if used over a sufficiently long period of time in a large number of patients will eventually result in increasing evidence of idiosyncrasy and untoward reactions. It, therefore, becomes of practical importance to have additional satisfactory preparations for the treatment of chronic congestive heart failure. Such a preparation should be at least as potent as those already available. It should be free of systemic toxicity and should produce relatively little local reaction at the site of injection. Mercumatilin satisfies these criteria. It is not only a safe and potent mercurial diuretic, but its local tolerance appears to be better than meralluride, which has been considered heretofore to be the least irritating of the preparations available for intramuscular injection.

SUMMARY

1. Mercumatilin (Cumertilin) and meralluride (Mercuhydrin) were compared as to predictability of diuretic response, degree of diuresis, safety, and local tolerance.

2. The predictability of obtaining a satisfactory diuresis with mercumatilin was found to be 59.1 per cent of 44 trials in 20 patients as compared to 58.5 per cent of 41 trials for 14 patients with meralluride.

3. Preliminary data suggest that the concomitant administration of acidifying salts is not as essential for a satisfactory diuresis with the use of mercumatilin as with the use of meralluride and other mercurial diuretics.

4. Mercumatilin is a safe and effective mercurial diuretic which is well tolerated upon intramuscular injection.

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Clinical Reports

NONTRAUMATIC AORTIC PERFORATIONS INTO GASTROINTESTINAL TRACT

Review of the Literature and Report of an Unusual Case

William G. Bagnuolo, M.D., and Hugh D. Bennett, M.D.

Hines, Ill.

NONTRAUMATIC perforations of the aorta into the gastrointestinal tract are an uncommon event, only 111 cases having been reported. Of the reported cases, sixty were due to carcinoma of the esophagus, forty-five to rupture of an aortic abdominal aneurysm, two to tuberculous perforation into the esophagus and aorta, two to tuberculous perforation into the duodenum and aorta, one to aneursym of thoracic aorta rupturing into the esophagus, and only one to duodenal peptic ulcer perforating into the aorta.

The case to be reported is of a type not heretofore recorded, namely, tuberculous perforation into lungs, aorta, and esophagus.

CASE REPORT

C. B., a 55-year-old Negro laborer, was admitted to the medical service of the Veterans Administration Hospital, Hines, Ill., with complaints of a head cold, fever, cough productive of a blood-tinged sputum, and an aching pain in the lower left chest of one week duration. He had been well until six months previously, when he noted chronic fatigue, a 30 pound weight loss, and night sweats. Additional history obtained from his wife three days after admission revealed copious hemoptysis on two occasions one week prior to admission productive of one-half and one pint of blood. No tuberculous contacts were known.

On admission the patient appeared well developed but chronically ill. His conjunctivas were pale; lymph glands were moderately enlarged but nontender. The lungs revealed no abnormality other than a few moist râles in the posterior portion of the left base. The heart size was within normal limits; there was a short systolic murmur at the apex; there were no thrills; and the blood pressure was 120/70 mm. Hg. The liver, kidneys, and spleen were not palpable. The abdomen was negative as was the rectum and prostate. There was, however, a marked wasting of the gastrocnemius-soleus muscles bilaterally. The neurological examination was negative.

At the time of admission, Jan. 14, 1950, the patient had an oral temperature of 102°F. He was white blood cell count 8,500 (83 per cent neutrophiles, 17 per cent lymphocytes). Urinalysis revealed a trace of albumin. Serology was negative, and repeated sputum examinations for acid-fast organisms were negative. A portable chest roentgenogram taken at the time of admission revealed fine, patchy infiltrations in both lung bases.

From the Veterans Administration Hospital, Hines.

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On the fifth hospital day, after the patient had received a total of 3,500 c.c. of whole blood, the red blood cell count was 3,550,000, hemoglobin 10 Gm. and white blood cell count 10,300 with a normal differential count. The platelet count was 198,000, bleeding time 2 minutes 45 seconds, coagulation time 5 minutes 30 seconds. A repeat portable chest roentgenogram revealed the lung fields clear but a prominence of the hilar shadows, bilaterally. Repeated electrocardiograms taken on the second, third, and fourth hospital days were not abnormal.

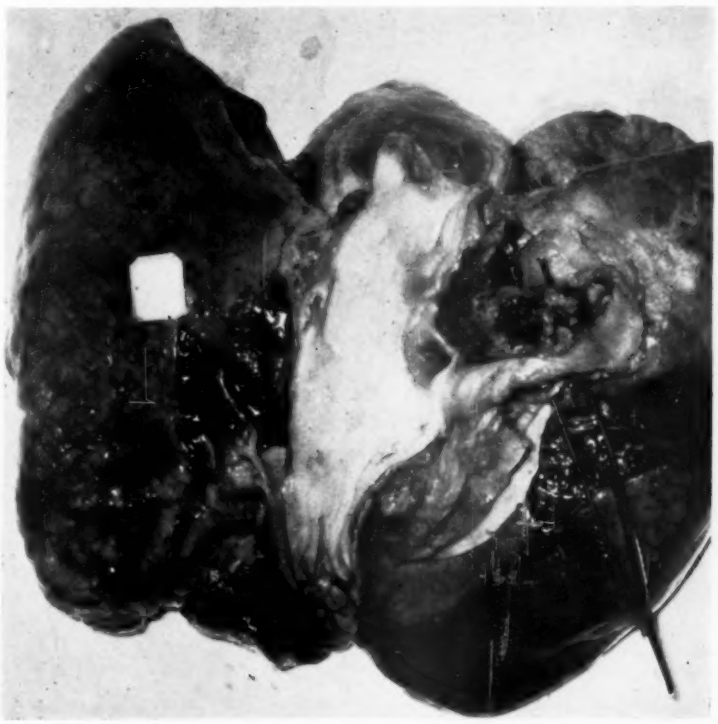

Fig. 1.—Tuberculous perforation into the aorta and esophagus, forceps lying in the perforation.

At the time of admission, Jan. 14 1950, the patient had an oral temperature of 102°F. He was isolated for possible tuberculosis and was placed on Crysticillin, 300,000 units, two times a day. The day following admission, the temperature dropped to 100.6° F., and the patient appeared somewhat improved. However, he suddenly complained of a severe compressing pain over the entire chest and went into a profound state of shock. He responded to morphine, atropine, oxygen, vitamin K, and whole blood, and his blood pressure rose to 108/88 mm. Hg from a previous low of 40/0 mm. Hg. On the third hospital day his condition seemed satisfactory; although his rectal temperature rose to 103° F. and then aureomycin therapy was started. The temperature began to decline, and the patient stated that he was feeling fairly well on the fourth hospital day. On January 19, five days after admission, the patient began to expectorate large quantities of bright red blood and died shortly thereafter.

Necropsy.—On opening the thorax, there was a mass measuring 5.5 by 3.5 by 3 cm. posterior to the aorta above the diaphragmatic surface, which was a laminated hematoma communicating through a perforation in the left lateral aspect of the descending aorta at this level. The perforation appeared punched out and measured 0.4 cm. in diameter. The hematoma was also attached to the lower end of the esophagus by fibrous adhesions. There was a perforation in the esophagus 2.5 cm. above the perforation of the aorta, which measured 1 cm. in diameter (Fig. 1). The hema-

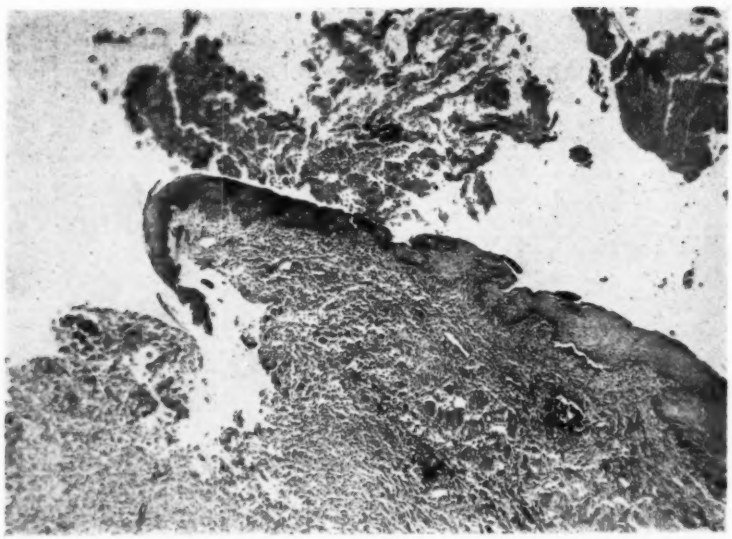

Fig. 2.—Microscopic section at the site of perforation of the esophagus with adjacent caseous tubercles.

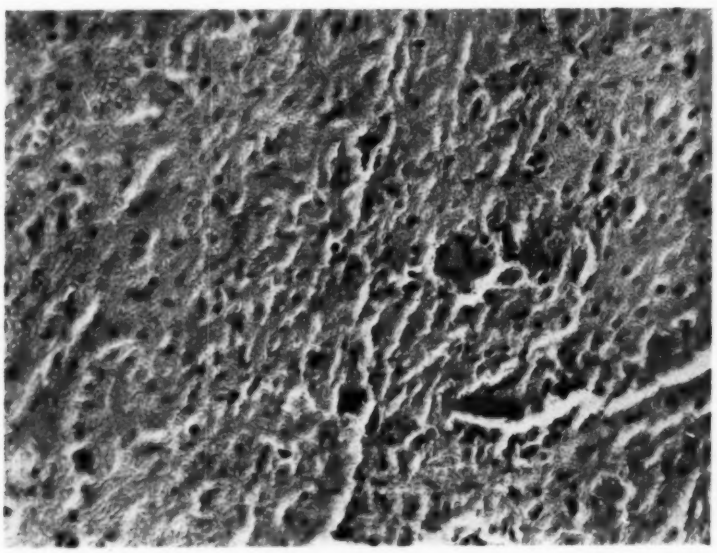

Fig. 3.—Microscopic section revealing tubercle from the adventitia of the aorta.

toma was adherent to the lower lobe of the right lung where there was a communication with one of the bronchi. There were several enlarged mediastinal lymph nodes, some of which were calcified, and some revealed, on section, a caseous grayish-white material. The stomach was markedly dilated and filled with 300 c.c. of clotted blood. The remaining gastrointestinal tract contained old, clotted blood. On cut section of the right lower lobe of the lung, there were numerous, small, nodular areas measuring up to 4 mm. in diameter, which were grayish-white in appearance and firm in consistency. The pleura over this area was dull and thickened.

Microscopic Examination.—There was a generalized miliary tuberculosis of all the abdominal organs with typical areas of tubercles and caseation. In the area of the perforation of the aorta the adventitia revealed several well-defined tubercles (Figs. 2 and 3): however, the media and intima presented only a chronic inflammatory process at the site of perforation. The mediastinal lymph nodes revealed well-defined tubercles, some of which were calcified.

COMMENT

The first case of rupture of the aorta into the gastrointestinal tract was reported in 1843 by Salmon.[21] He presented a case of aneurysm of the abdominal aorta rupturing into the duodenum. Although this was the first reported case, previous mention of the condition had been made by Chamel and Dalmas.[1] The first case of perforation into both gastrointestinal tract and aorta due to tuberculosis was reported in 1927 by Cadé and Dechaume.[12] There have been three subsequent reports.[13-15]

Of interest is the site of perforation. Of the 111 cases listed, sixty-three were into the lower one-third of the esophagus, five into the stomach, none into the first portion of the duodenum, one into the second portion of the duodenum, thirty-six into the third part of the duodenum, two into the jejunum, and four into undetermined or unestablished parts of the gastrointestinal tract.

It will be noted that perforation occurs only when pathological fixation of tissues occurs, as in carcinoma, perforating ulcer, tuberculosis, or where an anatomical factor is present. Thus, ruptured aneurysm into the gastrointestinal tract occurs at sites of anatomical fixation, as in the third portion of the duodenum and to a lesser extent in the esophagus, whereas in tuberculosis, carcinoma, and penetrating ulcer the esophagus is perforated wherever simple contiguity exists.

The symptomatology of rupture into the gastrointestinal tract is not specific but usually is that of the underlying disease. Massive hemorrhage as a terminal event occurred in 100 per cent of the cases, and 83 per cent had hematemesis. Neither melena nor any gross external evidence of gastrointestinal hemorrhage occurred in the remaining 17 per cent. In esophageal lesions all had hematemesis. Fifty per cent of gastric lesions had this symptom, but the numbers were small (four cases). Of the duodenal cases 75 per cent had hematemesis. It would be expected that the further down the gastrointestinal tract the rupture occurred, the less would be the incidence of hematemesis.

In this group of cases males predominated in a ratio of 6:1, reflecting only the difference in incidence of the causative disease and no other apparent special conditions. The age varied from 20 to 80 years, no children being reported.

Of special interest is the duration of life after the onset of first symptoms referable to actual establishment of continuity between the aorta and gastrointestinal tract. Contrary to expectations, survival for a period of days was the rule rather than the exception. There were immediate deaths in 32.7 per cent; 17.3 per cent survived a matter of hours, averaging 4½ hours, but 50 per cent survived an average of 11.03 days after the first signs of massive bleeding. The maximum survival was 60 days in the case of Schattenberg and Ziskind.[17]

SUMMARY AND CONCLUSION

1. A review of the literature from 1843 on revealed 111 cases of nontraumatic perforation of the aorta into the gastrointestinal tract.

2. The cases have been discussed under etiological factors, sites of perforation, most frequent symptoms, and findings.

3. An unusual case is presented in which the perforation of the aorta is on a tuberculous basis with perforation into the esophagus and right lung.

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RUPTURE OF AN ABDOMINAL ANEURYSM ASSOCIATED WITH MASSIVE GASTROINTESTINAL HEMORRHAGE

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IN 1943, Rottino[4] collected thirty-one cases of rupture of an abdominal aneurysm into the gastrointestinal tract, which, in addition to the case he reported, brought the total to thirty-two. In 1946, Hunt and Weller[2] added nine cases reported in the literature (including one of their own), which brought the total to forty-one. These were distributed as follows:

29 cases—third portion of duodenum
2 cases—second portion of duodenum
2 cases—duodenum (unspecified)
5 cases—stomach
2 cases—jejunum
1 case—small bowel.

New cases have been recorded following this report and, in addition, previously recorded cases have come to light.

	Cases	*Site of Rupture*	
(1) Bagozzi	1	Duodenum	1931*
(2) Hausman	1	Jejunum	1943
(3) Irwin and Frankel	1	Stomach	1945
(4) Ballice	1	Duodenum	1947
(5) Cleland	1	Jejunum	1947
(6) Scott, Grimes, and Maxwell	1	Stomach	1949†
(7) Baer and Loewenberg	1	Duodenum	1948*
(8) Pomerantz	1	Jejunum	1949

Total cases reported: 49.

Site of Rupture	*Cases*
(1) Duodenum	36
(2) Stomach	7
(3) Jejunum	5
(4) Small intestine	1

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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*Tuberculous false aneurysm.

†Case 6.

We are reporting a case of rupture of an abdominal aneurysm which clinically began with a massive gastrointestinal hemorrhage.

CASE REPORT

A 52-year-old city fireman entered the hospital on May 16, 1949, with complaints of a tender mass in his epigastrium, weight loss, and epigastric pain. The patient stated that he had consulted his family physician approximately one week prior to admission, and a gastrointestinal series was done which revealed no pathologic condition. The patient's present episode began on April 19, 1949, when he stated he had pain in his abdomen all day severe enough to cause him to perspire profusely. The pain was localized to the abdomen and apparently did not radiate. After April 19, 1949, the patient continued to have episodes of abdominal discomfort which were not related to food. There was an associated loss of appetite and a weight loss of 15 pounds.

Physical examination revealed an apprehenstive 52-year-old white man, who was moderately well nourished and moderately well developed. His average weight was 179 pounds, and the weight on admission was 159 pounds. Examination of the head and neck was negative except for Grade I sclerosis of the retinal arteries. Blood pressure was 210/115 mm. Hg, bilaterally. The heart rate was regular and slow. There was a systolic murmur heard to the left of the sternum and at the apex. A round, expansile, pulsatile mass was found just below the umbilicus, which measured 2 by 2 inches. When the patient was placed on his hands and knees, this mass was still palpable. There was a definite systolic bruit heard over the mass. The mass was movable and tender. There were excellent pulsations in all the vessels of the legs, and the blood pressure in the legs was normal.

Laboratory Examination.—The blood Kahn and blood Wassermann were negative. A urinalysis revealed a specific gravity of 1.005, hyaline, blood, and granular casts, with many white and red blood cells, and a one plus albumin. The red blood count was 3,300,000, with 10.4 Gm. of hemoglobin; the white blood count was 16,300, with 64 per cent neutrophiles, 25 per cent lymphocytes, 8 per cent monocytes, and 2 per cent eosinophiles. The sedimentation rate was 38 mm. per hour. The hematocrit was 42 volumes per cent. Repeat urinalysis revealed a persistent albuminuria, blood, granular, and waxy casts, and a specific gravity of 1.018. During the latter part of the hospital stay the blood nonprotein nitrogen was found to be 66 mg. per cent, and on repeat was 75 mg. per cent. Stool examination on one occasion revealed a trace of occult blood. In the terminal phase the CO_2 combining power was 62 volumes per cent, the blood NaCl was 465 mg. per cent, and blood chlorides 294 mg. per cent.

The chest roentgenogram and flat plate of abdomen were negative on admission. A barium enema revealed many diverticula in the sigmoid and descending colon. Lateral films of the abdomen were essentially negative. A terminal bedside flat plate of abdomen revealed moderate gaseous distention of the large bowel. Neither flat plate of the abdomen revealed any bony erosion.

Upon admission to the hospital the patient was ambulatory, although he complained of epigastric pain which required sedation and was not relieved by antiacids. At times, the patient complained of radiating pain from the epigastric mass to the right inguinal region. The day before a gastrointestinal series was to be performed, the patient suddenly vomited 3,000 c.c. of dark blood while at rest. The patient became pulseless, and the blood pressure could not be obtained. Immediate transfusions were given, and the patient rallied from this episode, although the blood pressure remained low as compared to the previous hypertensive levels. The patient continued to feel better for three days, during which time moderate abdominal distention was observed to be associated with suprapubic fullness. With the first episode of bleeding there was associated melena which was not noted at any later date. Three days later the blood pressure dropped suddenly, and continuous transfusions were again required. Following this second drop in blood pressure, a large, smooth, tender, doughy abdominal mass was palpable in the right lower quadrant which remained until the patient died. The patient's course was steadily downhill as he was apparently bleeding continuously, and the mass in the right lower quadrant apparently was increasing in size. During these latter episodes there was no objective evidence of gastrointestinal bleeding. Continuous transfusions were of no avail, and the patient died on the eighth day after the initial massive hematemesis.

Autopsy.—There were between 3,000 and 4,000 c.c. of bright red blood in the abdominal cavity with marked infiltration of the subcutaneous tissues and muscles below the umbilicus both anteriorly and posteriorly. The aorta contained many atheromatous plaques. One inch below the opening of the superior mesenteric artery there was an opening in the aorta 6 cm. long, which extended anteriorly into a saccular aneurysm (Fig. 1), which measured 10 cm. in diameter. There was a hole in the aneurysm which would admit the index finger and, when probed, extended into the root of the mesentery of the small bowel. The mesentery was greatly distended with clotted blood, and there was a defect in the mesenteric wall near the ligament of Treitz, over which the jejunum was firmly adherent. The jejunum was stripped away with much difficulty, but there was no defect noted post mortem in the mucosa of the bowel. The intestines were noted to be pliable throughout. There was no evidence of blood in the intestines at the time of death. The entire retroperitoneal area was grossly infiltrated with large amounts of clotted blood involving all structures, including the right psoas muscle. There was no additional defect found in the gastrointestinal tract.

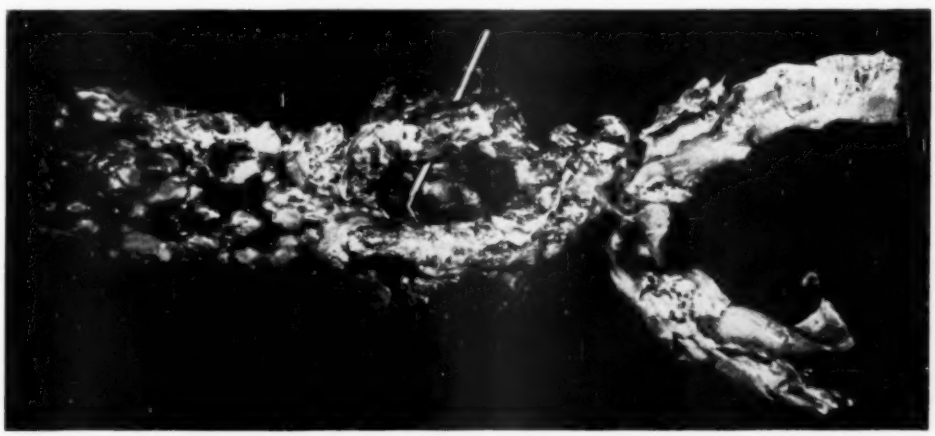

Fig. 1.—Showing a saccular aneurysm of the lower abdominal aorta and communication between the sac and the root of the mesentery.

DISCUSSION

Clinically, the authors thought that this was a case of rupture of an abdominal aneurysm into the gastrointestinal tract.

The cases previously reported of rupture of an abdominal aneurysm with massive gastrointestinal hemorrhage were associated with a direct communication between the aneurysm and the gastrointestinal tract. The case reported above revealed no evidence of a communication at the post-mortem examination, although the jejunum was firmly adherent to the defect in the mesentery through which the aneurysm ruptured into the abdominal cavity. It seems quite unlikely that if a communication had existed, it would have healed in the eight days following the gastrointestinal hemorrhage. The root of the mesentery, however, was distended with large amounts of dark clotted blood and communicated with the peritoneal cavity and the perforation in the aneurysm. The most probable explanation in the opinion of the authors and the pathologist was that the contents of the distended mesentery obstructed venous return of the portion

of the jejunum described, with subsequent rupture of a large venous channel into the lumen of the jejunum. The initial hemorrhage into the gastrointestinal tract was unusual in that it occurred as an early manifestation of the rupture and did not recur in the following eight days prior to death. Following the initial gastrointestinal hemorrhage, the patient apparently continued to bleed retroperitoneally and along the right psoas muscle. This was substantiated by the appearance of a mass in the lower right quadrant three days following the initial gastrointestinal hemorrhage and a repeat fall in blood pressure.

SUMMARY

This is a case report of a massive gastrointestinal hemorrhage as the initial manifestation of a rupture of a saccular abdominal aneurysm. This case is unusual in that clinically the massive hematemesis indicated rupture into the gastrointestinal tract, but this was not confirmed at post-mortem examination. An explanation for the gastrointestinal hemorrhage is offered by the authors.

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SPONTANEOUS HYPERPOTASSEMIA AS A CAUSE OF DEATH IN DIABETIC ACIDOSIS

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DIABETIC coma is one of the most widely recognized and widely treated conditions in which potassium depletion occurs. This has been demonstrated by the many metabolic balances and clinical reports in the recent literature.[1-5] As the condition is so amenable to treatment, some clinics are now administering added potassium to repair and maintenance solutions routinely.

For practical purposes the body depletion of potassium may be divided into two phases. These are, first, the movement of potassium from the body stores into the serum; and, second, the disposal of serum potassium with excretion chiefly in the urine[6] and the return to the cells. In mild cases these undoubtedly interlace, but in severe cases with hemoconcentration, shock, decreased renal blood flow, and decreased glomerular filtration rate, the disposal of the serum potassium may be delayed. Therefore, it is plausible that potassium could rapidly increase in the extracellular fluid, perhaps to a dangerous degree. Movement of potassium from the cells is associated with dehydration,[7] cell breakdown according to the potassium/nitrogen ratio,[8] a migration of intracellular base to decrease the extracellular acidosis,[9] and the movement of potassium with depletion of the liver and muscles of glycogen.[10] Early in diabetic coma, high levels have been reported,[11,12] but these are not necessarily related to shock.[11] Bellett and associates have demonstrated, however, that depletion of the cell and serum occurs within a matter of hours following treatment regardless of the initial levels.[11] The lowered serum values resulting from the predominance of phase two may be partially accounted for by stabilization of the circulation and the formation of urine in sufficient amounts to cause the desired diuresis. Potassium is deposited in the cells with glycogen[13] and protein,[14] and this is facilitated by insulin.[15] Expansion of the extracellular compartment[16] will account for further loss, and this usually is aggravated by potassium-free solutions.[17] Isotonic saline is also believed to be a cause of potassium loss when administered in large amounts.[18] Vomiting may also aggravate the potassium loss,[19] although it reduces the serum acidosis. Thus it may be seen how potassium first leaves the cell and is redistributed by way of the serum. The following presentation demonstrates a case of death probably due to potassium intoxication. It seems that only the initial group of factors functioned here, as death ensued very rapidly before any treatment could be instituted.

From the medical service of the Memorial Hospital, Wilmington, Del.
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CASE REPORT

R. E. was a 29-year-old white truck driver who was admitted to the medical service of the Memorial Hospital on June 20, 1949. He was a known diabetic of three years duration and had

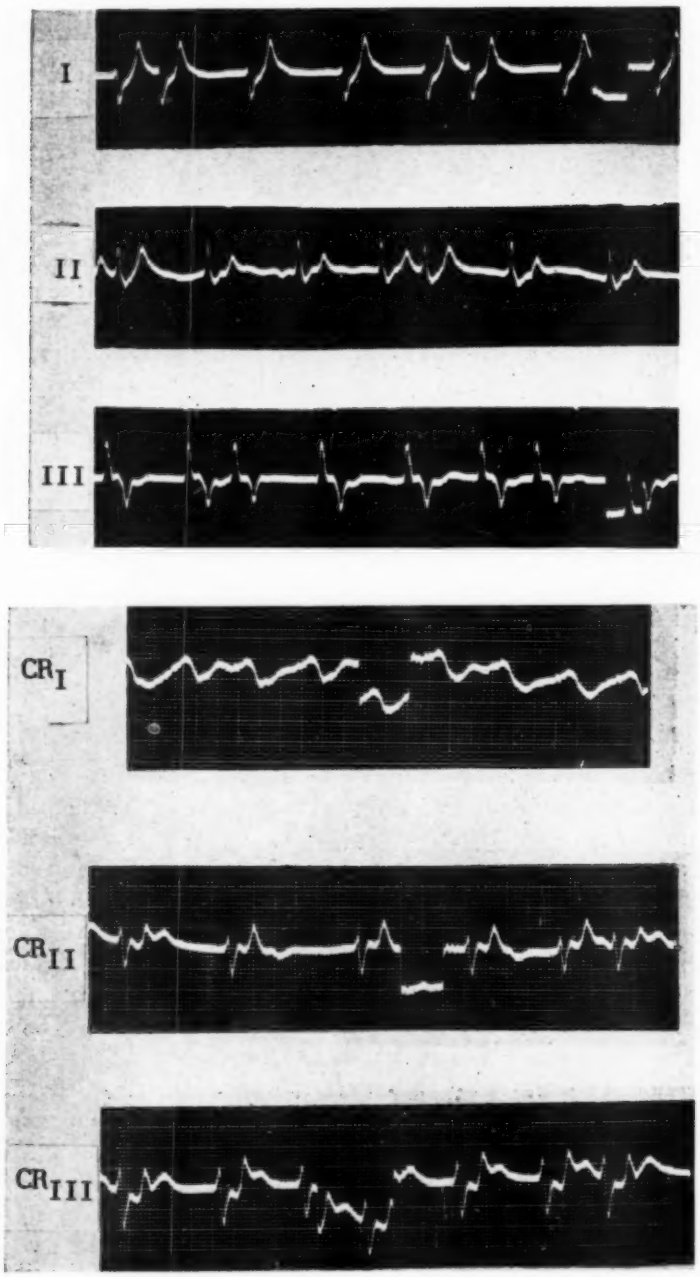

Fig. 1.

been taking forty units of protamine zinc insulin daily for the past year. His diet consisted only of limitation of sweets. Thirty-eight hours before admission the patient drove about 500 miles and remarked that the cab of his truck was extremely warm. Twelve hours before admission he noted nausea and passed three large, loose stools associated with abdominal discomfort. He was seen by the local physician at that time, and he was given an amount of protamine zinc insulin, the dosage of twenty units not being known until after the patient's death. He remained restless all night and noted dryness of the mouth. He was seen on the morning of his death by the local physician who advised hospitalization for diabetic acidosis.

Upon admission the patient showed marked dehydration, weakness, and some confusion, but there was no loss of consciousness. The skin was hot and dry. The blood pressure in both arms was 80/50 mm. Hg. The heart showed an irregular rhythm with distant sounds, but the lungs were clear. There were no masses or tenderness in the abdomen. The extremities showed no edema. There was no scent of acetone on the breath, and the eyeballs were neither sunken nor soft. With the history obtained, the most probable diagnosis was diabetic acidosis. An electrocardiogram was taken immediately (Fig. 1). Essential blood studies were done but were not reported until after death. Insulin and saline were ordered until a transfusion could be started. Before the parenteral fluids could be obtained, the patient lapsed into unconsciousness and died in less than twenty minutes from the time of admission. The death was very sudden, as clinically the patient had looked fairly well in spite of the early shock state. The diagnosis of diabetic acidosis was verified by the chemical determination which showed a blood sugar of 370 mg. per cent, blood urea nitrogen of 65 mg. per cent, and a carbon dioxide combining power of 14.7 volumes per cent.

Before the electrocardiogram was seen, it was thought that the patient had died of a coronary thrombosis. The electrocardiogram, however, showed peaking of the T waves, absence of the P waves, widening of the QRS complex, and a slow rate with intermittent ventricular fibrillations. This was interpreted as severe potassium intoxication.[22]

At post mortem only the usual post-mortem changes were noted. There was no macroscopic or microscopic evidence of coronary infarction on serial sections. At autopsy (one hour after death) blood was taken from the ventricle for sodium and potassium determinations. Readings showed a sodium of 96 m eq. per liter and a potassium of 14 meq. per liter.

DISCUSSION

The action of potassium on the heart was first described by Ringer in 1896.[20] Thomason later, in 1936, showed the mode of action and its direct influence on the heart.[21] Winkler, Hoff, and Smith then demonstrated the relationship of rising serum potassium levels to the electrocardiogram in dogs,[22] and in recent literature there have been cases of death related to potassium intoxication.[23,25] This, however, has been seen most commonly in severe renal disease and most often in the stage of oliguria. An agonal rise in potassium has been described by some observers, but this is by no means a constant finding.[24,26,27]

In this case the initial dehydration was caused by excessive heat. This, associated with exertion and poor diet, may have caused the acidosis. Probably much sodium was lost through the skin, as the extracellular sodium does not routinely appear extremely low in diabetic acidosis.[28] It is not likely in this case that there was a cellular migration of sodium, although it is known that one-half of the total body sodium may migrate into the cell in face of severe cellular potassium depletion.[29] Darrow states that one cannot survive when over one-half of the body sodium is depleted,[30] and our observations of levels this low have all been in terminal cases, at times without explanation for such a hyponatremia. With the decreased serum sodium, the severe dehydration, and the early and rapidly pro-

gressing shock, one may assume that there was a decrease in glomerular filtration rate. Therefore, as cell breakdown proceeded, as glycogen was moved from the muscle and liver, the serum level of potassium rose to a sufficiently high level to cause death. The history, physical examination, type of death, and serum readings, correlated with the ante-mortem electrocardiogram, justify this case presentation as a potassium death.

Thus it is again stressed, although diabetic acidosis is a common disorder associated with a low potassium, that it is absolutely necessary for one to stabilize the circulation and have an adequate urine flow before potassium therapy is instituted.

As the blood was drawn from the ventricle post mortem in this case, we ran a small series of determinations on post-mortem blood from one to twenty-four hours old. We noted no levels higher than 7.5 meq. per liter, even in severe renal disease. One sample read 12 meq. per liter from a chronic case of nephritis in which the serum and cells were not separated for thirty-six hours. Blood from the blood bank displays a slow breakdown[31] with the liberation of potassium, and we noted in one pint ten days old that the level had reached 60 meq. per liter.

SUMMARY

Initially in diabetic acidosis the serum potassium may be elevated. A case of diabetic acidosis is reported in which the serum potassium rose spontaneously to a level high enough to produce a cardiac death. Thus, it is emphasized that the circulation should be stable and the urine should be flowing before potassium is given to a diabetic in acidosis.

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Review of Recent Advances

THE CLINICAL VALUE OF THEOPHYLLINE IN HEART DISEASE*

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THE clinical use of theophylline salts as adjunctive treatment in heart disease has rested largely on their properties as myocardial stimulants, diuretics, and coronary vasodilators. In addition, theophylline has proved of value in the management of bronchial asthma as an effective bronchodilator. Nevertheless, there has been some divergence of opinion concerning the mechanisms of action of the drug on the cardiovascular system and its resulting therapeutic effectiveness. In 1936, the Council on Pharmacy and Chemistry of the American Medical Association[1] discussed the status of theophylline ethylenediamine. The Council continued claims for the drug as a myocardial stimulant and diuretic, but it further decided that there was no basis for claims of efficacy as a coronary vasodilator nor as a means of controlling cardiac pain. Goodman and Gilman[2] were vague regarding the value of theophylline salts in cardiovascular disease. They recognized some cardiac and peripheral vascular effects as of probable limited value. On the other hand, the clinical and experimental evidence offered by a number of workers[3-8] indicates that theophylline might be regarded as therapeutically valuable, particularly in congestive heart failure and acute pulmonary edema. It is the purpose of this review to re-examine the pharmacologic and clinical action of theophylline salts in the hope that the position of theophylline in the management of heart disease may be clarified. It is based on clinical and experimental studies previously published.[9,10,11]

MYOCARDIAL STIMULATION

Starr and co-workers[12] concluded from the effect of theophylline upon the cardiac output that the drug was a powerful myocardial stimulant. They believed that clinicians had underestimated this action because they failed to note an effect upon pulse rate, respiratory rate, and blood pressure, functions not affected by theophylline. More recently, Howarth, McMichael, and Sharpey-Schafer[8] and Fowell and co-workers[13] again reported an increase in cardiac output associated with a fall in venous pressure and right ventricular filling pressure. Our findings support this view. Table I represents the findings from a typical experiment in a heart-lung preparation.

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TABLE I.

EVENT	CARDIAC OUTPUT (C.C.-MINUTE)	BLOOD PRESSURE	RIGHT AURICLE (CM. H_2O)	LEFT AURICLE (CM. H_2O)	VENTRICULAR DIAMETER (CM.)	RATE	CORONARY INFLOW PER CYCLE (C.C.)	CORONARY INFLOW MINUTE (C.C.)	REMARKS
Control	630	95/60	4.4	4.9	5.5	166	0.23	38.1	
Chloral hydrate 0.8 Gm.-12M	—	—	—	—	—	—	—	—	
Heart failing	480	90/60	6.6	11.0	6.7	111	0.35	38.8	Pulmonary edema and congestion
Theophylline 3 minutes	600	100/60	5.5	6.6	5.5	115	0.32	36.8	Myocardial stimulation; pulmonary edema subsides

Cardiac output, arterial pressure, right auricular and left auricular (venous) pressures were measured directly. (The right auricular pressure was less significant because it was partly determined by the flow from the reservoir which was of fixed height.) The ventricular diameter was measured directly, the rate and the coronary flow were both measured directly per beat, and the coronary minute flow was calculated, using the Gregg-Green differential pressure flowmeter. The heart was made to fail with chloral hydrate. It was believed that heart failure thus obtained resembled in its mechanical aspects clinical congestive failure. It was characterized by decreased cardiac output, increased venous pressure, especially from the left auricle, and cardiac dilatation. The total coronary flow was not much changed. The administration of theophylline in doses approximately those used clinically resulted in an increase in cardiac output, the heart assumed its former diameter, and the venous pressure fell, while the coronary circulation was not much affected.

The heart was made to fail by chloral hydrate intoxication. Theophylline in doses approximating those used clinically resulted in an increase in cardiac output, return of the dilated heart to its original size, and fall in venous pressure. The coronary circulation was not affected. The myocardial effect began immediately and lasted less than one-half hour.

The effect of theophylline on the venous pressure has been studied clinically. It was known that the venous pressure was lowered by theophylline.[14,15] However, before reaching conclusions on this point, it was necessary to consider spontaneous variations of the venous pressure. These may be considerable. By modifying the original method of Moritz and Tabora,[16] it was possible to take repeated readings without reinserting the needle.

The variability of venous pressure is shown in Table II. It was compared with the changes which occurred following the intravenous injection of 0.5 Gm. of theophylline. The results are given in Table II.

TABLE II.

FALL IN VENOUS PRESSURE (MM. OF WATER)	CONTROL GROUP (NO. CASES)	THEOPHYLLINE AMINOISOBUTANOL GROUP (NO. CASES)	AMINOPHYLLINE GROUP (NO. CASES)
1 to 19	35	7	4
20 to 39	24	16	4
40 to 59	3	9	8
60 to 79	3	6	2
80 to 99	0	1	2
100 to 119	0	0	1
120 to 139	2	0	0
Total number	67	39	21
Range	2 to 128	8 to 77	11 to 118
Mean	23.6	36.7	48.0
Standard deviation	22.3	16.5	27.8
Median	18.0	33.0	48.0
Difference of means: Standard error		3.47	3.67

In the control group the fall of venous pressure was measured from the highest to the lowest reading obtained. When drugs were given, it was measured from the reading just before the drug was administered to the lowest reading obtained within thirty minutes.

Theophylline aminoisobutanol contains approximately 67 per cent of theophylline. The theophylline content of aminophylline (U.S.P.) varies from 75 to 82 per cent.

From these data it may be seen that the decrease which follows the drug significantly exceeds the spontaneous variations. It seemed probable that myocardial stimulation was at least one of the causes of the observed drop in venous pressure as these two phenomena occurred concomitantly in the heart-lung preparation.

Associated with the drop in venous pressure, theophylline also produced shortening of the circulation time. The first reading was taken shortly before the drug was administered, the second reading about fifteen minutes afterwards. The results are summarized in Table III.

TABLE III.

DRUG	NO. CASES	DOSE (GM.)	AVERAGE SHORTENING OF CIRCULATION TIME (SECONDS)
Theophylline aminoisobutanol	9	0.24	10.4
Theophylline aminoisobutanol	20	0.48	12.8
Aminophylline	9	0.48	16.8

The longer the original circulation time the greater was the shortening observed. Changes of the circulation time of more than five seconds were always associated with a significant decrease in venous pressure. However, in eleven cases the venous pressure fell while the circulation time remained unchanged.

EFFECT ON THE CORONARY CIRCULATION

The effect of theophylline on the coronary circulation is much more difficult to evaluate. Goodman and Gilman[2] conclude from available evidence that theophylline causes relaxation of the coronary vessels in the experimental animal. Mokotoff and Katz[6] noted that treatment with theophylline reduced the size of experimentally produced myocardial infarcts in dogs, and that the collateral vessels appeared dilated. This view appears to be generally acceptable. The difference of opinion arises on the questions of whether the increase in coronary flow results directly from coronary dilatation or is secondary to myocardial stimulation. Furthermore, it is questionable whether observations made in the physiological laboratory can be applied clinically to patients with coronary sclerosis. This becomes especially doubtful if the drug is given by mouth and thus is less effective.

None of the findings in the literature (Essex and associates[17] and Stoland and associates[18]) indicate that the coronary dilatation is necessarily a drug effect on the arteries themselves. Boyer and Green's[19] findings that myocardial stimulation following xanthines preceded the increase in coronary flow would support the view that improvement in coronary flow is secondary to improved myocardial function. Foltz and co-workers[20] found that aminophylline actually intensified myocardial anoxia. Although this drug dilated the coronary vessels, it also stimulated the myocardium to such an extent that the increased blood flow could not keep up with the excessive demand, and venous oxygen saturation fell. Our own experiments in the heart-lung preparation also fail to show evidence that theophylline directly dilates the coronary arteries.

The physiological evidence for considering theophylline a direct coronary dilator of therapeutic value is therefore uncertain. Furthermore, in coronary disease the vessels are often calcified and rigid and appear not to be very amenable to dilation. Also, coronary disease is often treated with theophylline given by mouth whereby the effect is much weakened. It is therefore not surprising that the most careful observations have failed to indicate that theophylline given by mouth influences the course of angina pectoris.[9,21,22] None of the opinions to the contrary are based upon facts as well controlled as these.

EFFECT ON PERIPHERAL VESSELS

Xanthines are powerful dilators of peripheral vessels. The available data appeared to be so conclusive that we accepted them without further experiments. By oncometric studies and perfusion experiments great increase in blood flow has been demonstrated in the kidney,[23,24,25] spleen,[25] and in the extremities.[24,26] Stewart and Jack[27] examined the evidence of vasodilation after theophylline by measuring the skin temperature. They found that the presence of heart disease and congestive failure did not affect the vasodilation which they demonstrated. It is entirely probable that this peripheral effect is partly responsible for the fall in venous pressure following theophylline even though there is no conclusive proof for this assumption.

EFFECT ON THE PULMONARY CIRCULATION

Bock[26] found a marked increase in the perfusion volume through the isolated normal lung after theophylline. Friedberg, Katz, and Steinitz[28] found an increase in stroke volume and suspected the possible presence of pulmonary vasodilation. Smith and Jensen[10] found that in the de Barenne preparation in which congestion of the lung had been produced by failure of the left ventricle, theophylline greatly increased the flow through the lung after the heart had stopped. This effect was attributed to a vasodilator effect by theophylline. The effect which the failing heart as such might have had upon the pulmonary circulation is under study.

TABLE IV.

PULMONARY BLOOD FLOW-CONTROL	LUNG CONGESTED; HEART STOPPED	AFTER THEOPHYLLINE; NO HEART BEAT
321 c.c. per minute	191 c.c. per minute	256 c.c. per minute
400 c.c. per minute	300 c.c. per minute	360 c.c. per minute

Pulmonary flow in the de Barenne preparation after the lung had been congested as a result of left ventricular failure. The flow decreased. The heart was allowed to stop completely. Theophylline was added to the perfusing blood with the result that pulmonary flow again was greatly increased and congestion and edema rapidly disappeared.

THE EFFECT ON VASCULAR PERMEABILITY

It is frequently mentioned in the literature that purines affect the membrane permeability of the blood vessels (e.g., Sollmann[29]). These statements are based mostly on older work, and such papers as were consulted showed a lack of satisfactory controls. Steinberg and Jensen[11] tested the concentration of Evans blue in the plasma of patients with congestive heart failure. Following the injection of theophylline the venous pressure fell, but the concentration of dye remained the same, indicating that water had not left the circulating blood. Thus, they found no evidence that theophylline caused a change in vascular permeability. They were, however, concerned with the immediate effects con-

comitant with the changes in venous pressure and circulation time and not with the diuretic effect which probably occurs later.

THE THERAPEUTIC VALUE OF THEOPHYLLINE IN HEART DISEASE

Theophylline strengthens the myocardium. In this respect, its action is similar to that of digitalis. It produces peripheral vasodilation and enhances the circulation through the congested lung and probably through other organs.

In congestive heart failure these changes would be expected to result in temporary improvement as expressed by shortening of the circulation time and by a decrease of the elevated venous pressure. These were changes actually found at the bedside.

The therapeutic value of theophylline appears to be in situations where myocardial stimulation and circulatory relief are urgently required. It seems advantageous to combine it with digitalis to tide over the heart until digitalis could become effective. It may also be used in cases where digitalis, for some reason, cannot be given.

The effect on the pulmonary circulation renders it valuable whenever this circulation is impaired. It therefore has an additional value in left ventricular failure, both in cardiac asthma and pulmonary edema.

Apart from this, theophylline, like most purine derivatives, has a stimulating effect upon the central nervous system which gives the patient a feeling of well being. This must not be mistaken for a cardiovascular effect. This point should particularly be remembered when studying the effect of small daily doses in coronary disease.

SUMMARY

1. In the heart-lung preparation, when the heart was made to fail with chloral hydrate, theophylline produced an increase in cardiac output, return of the dilated heart to its original size, and fall in venous pressure.

2. In patients in congestive heart failure, theophylline in the usual dosage caused a significant fall of venous pressure and a shortening of the abnormally prolonged circulation time.

3. The effect upon the coronary circulation is uncertain. The coronary vasodilation frequently observed may be secondary to myocardial stimulation. It has not been possible to demonstrate an effect upon the course of angina pectoris by giving theophylline by mouth.

4. Theophylline has a dilator effect upon peripheral blood vessels. This may be a factor in the lowering of venous pressure.

5. Theophylline increases the pulmonary circulation, especially when the lungs are congested from the left ventricular failure.

6. It has not been demonstrated that theophylline changes vascular permeability.

7. The therapeutic uses of the drug are discussed.

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